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of the

SOUTHERN SURGICAL ASSOCIATION

AT HOT SPRINGS, VA.

DECEMBER 10-12, 1946

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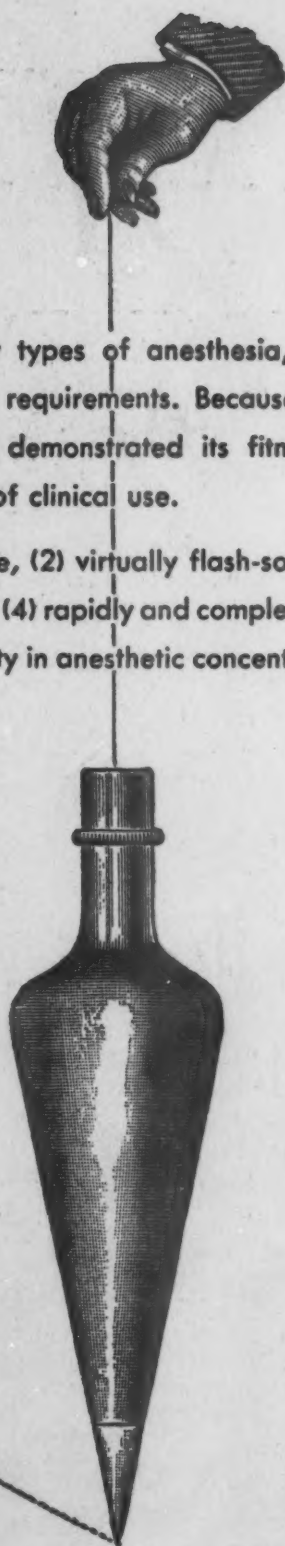
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ANNOUNCEMENT



The J. B. Lippincott Company announces with regret the resignation of Dr. Walter Estell Lee as Chairman of the Editorial Board of the ANNALS OF SURGERY. The editors join with the publishers to express their deep appreciation of his keen leadership over the past twelve years. His selective experience and sound surgical judgment have contributed much to making the ANNALS OF SURGERY of increasing value to the practicing surgeon and to the growing number of younger men who are rising into the specialty.

The publishers wish also to announce that at a recent meeting of the Board, Dr. John H. Gibbon, Jr., of Philadelphia, was elected Chairman of the Editorial Board. Dr. Gibbon, who is Professor of Surgery and Director of Surgical Research at Jefferson Medical College, Surgeon to Jefferson Medical College Hospital and the Pennsylvania Hospital, besides being Recorder of the American Surgical Association, brings to this position a wide background and leadership in surgery.

Coincident with this change it is planned that the ANNALS OF SURGERY will broaden its editorial supervision by creating an Advisory Board. Senior men, as they may resign or reach retirement, will be invited to remain in this advisory capacity so that the ANNALS OF SURGERY may continue to benefit from their wisdom and wide experience. As new appointments are made by the publishers as a result of conferences with the senior men and Dr. Gibbon, as Chairman of the Editorial Board, these new men will have the advantage of consulting with this senior body for advice and opinion.

PLEASE NOTE



NEW EDITORIAL ADDRESS

Original typed manuscripts and illustrations submitted to this Journal should be forwarded prepaid, at the author's risk, to the Chairman of the Editorial Board of the ANNALS OF SURGERY.

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1025 Walnut Street, Philadelphia 7, Pa.

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TRANSACTIONS OF THE SOUTHERN SURGICAL ASSOCIATION

MEETING HELD AT HOT SPRINGS, VA.
DECEMBER 10-12, 1946

THE MORTALITY OF SURGICAL DISEASE*

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AS ALL SURGEONS KNOW, in 1946 the patient requiring the attention of a surgeon has a much better chance for recovery than he has ever had before. It may seem presumptuous to present evidence before this body that this is true or to develop figures measuring to what degree it is true. However, there are certain implications arising from the current steady decline in surgical mortality that are frequently ignored or misinterpreted by medical writers, both surgeons and nonsurgeons. The purpose of this paper is to present the curve of annual surgical hospital mortality at the University of Virginia Hospital over a period of 12 years, and to discuss its significance. The results are recorded with a pride of accomplishment in surgery which is not exclusively local. As the result of contributions to medical knowledge throughout the world, the same progress could be demonstrated in every progressive surgical clinic.

The decrease in surgical mortality to be demonstrated is, of course, the result of revolutionary improvements in surgical practice during the last generation, improvements that have had a steady acceleration so that the last five years have seen the greatest gain of all. The 12 years under scrutiny

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

here represent the accretion of advances of many preceding years. These developments in surgery have been largely directed toward the more complete protection of the surgical patient as a whole from the effects of both disease and operation.

We need not discuss in detail any of the factors which make up the total pattern. There are at least six major elements to be mentioned, not necessarily in the order of their relative importance: (1) An increase in the accuracy of the diagnosis of disease and particularly of the diagnosis of surgical complications, such as thrombophlebitis and shock. (2) A stricter attention to and a more accurate management of water, electrolyte, protein and vitamin balances in the surgical patient. (3) A better understanding of the rôle of blood volume and its control. (4) Major developments in the field of anesthesia and in the mechanical control of respiratory complications. (5) The introduction of specific chemotherapeutic and antibiotic substances. (6) The adoption of certain special therapeutic measures in common surgical diseases, such as those developed for the treatment of phlebothrombosis, thrombophlebitis, jaundice, thyrotoxicosis, intestinal obstruction, and others. The first five of these affect the chance of recovery of any patient with major surgical disease. The sixth has its influence on general surgical mortality by protecting the individual patient suffering from a specific condition.

MATERIAL

We report the over-all mortality in 20,137 cases cared for by the Department of Surgery and Gynecology of the University of Virginia over a period of 12 years (1934 to 1945, inclusive). These cases include all direct admissions to the surgical service, whether or not operation was performed.* As in any surgical service, operative cases represent an overwhelming majority of the total number. The operations were performed in more than half of the total number of cases by resident surgeons, men in the fifth or sixth year of graduate training or, in the less exacting material, by assistant residents under the supervision of the resident. In all ward cases the decisions were made by a visiting surgeon, and in practically all major operative cases from the wards the exposed pathologic changes were observed by a visiting surgeon and the choice of surgical management determined by him in consultation with the operator. Under this supervision the resident staff performed almost all the major surgical operations on ward patients. Preoperative preparation, postoperative care and the treatment of nonoperative cases were closely followed by visiting surgeons in daily rounds.

During the period reported no striking changes occurred in the type of material admitted to the surgical service with the exception of a marked increase in major thoracic surgery. During this period also, as will be noted later, the threshold of operability was progressively lowered.

* Transfers to the surgical service are not included. The mortality figures, therefore, have relative rather than absolute values.

The yearly number of deaths has been calculated as a percentage of each year's cases, constituting the surgical mortality for that year. The mortality percentages have been separately calculated also for each six-year period.

A comparison of the over-all mortality with that of a single illustrative condition appeared useful. For this comparison mechanical intestinal obstruction was chosen, in the first place because it has a relatively large mortality rate in which any change could be more confidently interpreted and in the second place because the data were readily available from a general study of the subject under preparation by one of the authors. The mechanical intestinal obstruction material consists of all cases so diagnosed during the period, whether or not operation was performed.* In order to obtain significantly large figures, the mortalities were calculated on each half of the total material rather than yearly. For the first six-year period there were 147 cases of intestinal obstruction and for the second, 186 cases.

RESULTS

The curve of annual percentages of surgical deaths (Chart 1) shows an almost continuous drop from the beginning of the period to the close, descending from a high of 7.1 per cent in 1934 to a low of 2.5 per cent in 1945. This represents a decline of almost two-thirds in the absolute values. If one compares the first six years with the remaining six years, the average figures are 6.3 per cent for the former as compared to 3.4 per cent for the latter (Table I), a decline of 46.1 per cent (Chart 2).

During the first six years the mortality from intestinal obstruction was 27.2 per cent, and during the last six years, 15.0 per cent (Table I). This represents a decline in mortality of 44.9 per cent (Chart 2), which is almost exactly the corresponding decline in mortality for all cases admitted to the surgical service.

DISCUSSION.—The literature abounds with reports of steadily improving mortality rates in specific surgical diseases, both with and without operation. We have been able to find no report presenting even a rough over-all picture such as we have presented except for data scattered in relatively inaccessible annual reports of hospitals. Without the more detailed analysis to which the figures might be susceptible, there can be derived from them at least four implications that should be a part of current surgical thought.

An obvious result of declining surgical mortality has been the expanding surgical horizon, particularly the invasion of new fields and the lowering of the threshold of operability. It is now justifiable to undertake surgical operations of an extent that a generation ago no surgeon would have even considered. It must be noted again that the period studied coincides with a period of great increase both in number and extent of intrathoracic proce-

* A few cases of relatively rare occurrence presenting special problems were excluded from the data reported. These were instances of congenital atresia, Hirschsprung's disease, fecal impaction, benign rectal stricture and malfunctioning colostomy.

dures. It also coincides with a general surgical trend towards a more radical approach to cancer and particularly to intra-abdominal cancer. One need only cite the extensive resections for cancer reported by Brunschwig,¹ Lahey,² and others, as well as expansion in limits of operability, such as that presented by David and Gilchrist³ for cancer of the rectum. These are only examples to illustrate the point. A similar trend has been obvious in the surgical approach to cancer at the University of Virginia Hospital. We are not immediately concerned with the justification for multiple visceral resection for abdominal

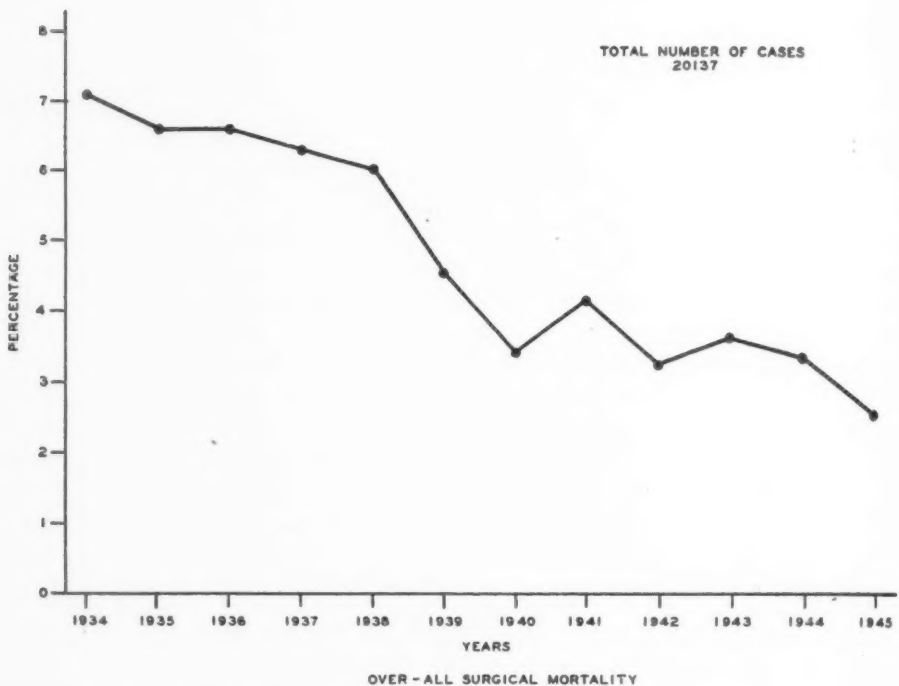


CHART 1.—Annual hospital mortality, Department of Surgery and Gynecology, University of Virginia Hospital, 1934 through 1945, including all cases (20,137) treated with and without operation.

cancer, but solely with its relationship to total hospital mortality. In spite of the fact that these developments in surgery have been taking place, developments theoretically to be expected to increase mortality, that phenomenon has not occurred. The decline in surgical mortality would unquestionably have been even more dramatic if these bold ventures had not been undertaken.

In the measurement of improvements in the surgical mortality of specific diseases and particularly of specific diseases studied in relation to new therapeutic devices, the curve of total surgical mortality has a continuing significance. Brooks⁴ compared the mortality of surgical operation in the aged

MORTALITY OF SURGICAL DISEASE

with the life-expectancy of the general population in the same age-group. Balfour⁵ presented before this society the late results of surgery in cancer of the stomach against the background of a similar life-expectancy curve. Other studies of a like nature have been made, all of which illuminate the significance of surgical results. Many reported instances of improvement in surgical mortality have been ascribed to the adoption of individual therapeutic procedures without measured consideration of the results to be expected without such procedures. An hypothetic example may be given. In our own treatment of intestinal obstruction a drop of almost 50 per cent occurred in the mortality when two six-year periods were compared. During the later period, following the report of Fine, Hurwitz and Mark,⁶ plasma adminis-

TABLE I

ACTUAL MORTALITY OF ALL CASES AND OF CASES OF INTESTINAL OBSTRUCTION IN THE YEARS 1934-1939, INCLUSIVE, AS COMPARED TO THE YEARS 1940-1945, INCLUSIVE. THESE FIGURES REPRESENT BOTH OPERATIVE AND NONOPERATIVE CASES.

Years	All Cases		Intestinal Obstruction	
	Number	Mortality	Number	Mortality
1934-1939.....	8,251	6.3%	147	27.2%
1940-1945.....	11,886	3.4%	186	15.0%

tration was introduced as an adjuvant to other therapy in small bowel obstruction. It would be easy to ascribe to this measure a major influence in the improvement in results were it not that the mortality of other surgical disease dropped correspondingly. In the light of that comparison any effect of plasma administration cannot be descried. In other words, statistical appraisal of surgical procedures should not be attempted without either employing the alternate case method in a large series, or with a full knowledge of the total decline in surgical mortality in the individual institution during the period studied.

Harvey Cushing, at the time he took over the professorship at Harvard and the surgical direction of the Peter Bent Brigham Hospital, wrote in a letter to his colleague, Dr. Christian, as follows⁷: "I would like to see the day when somebody would be appointed surgeon somewhere who had no hands, for the operative part is the least part of the work." This rhetorical exaggeration from a man whose hands were swift instruments of extraordinary accuracy and delicacy expresses a truth of which a hint is seen in the present data. The material presented, as already stated, consists in more than half the cases of operations of all magnitudes carried out by relatively inexperienced technicians, the residents, under the supervision of experienced surgeons. Since the decline in surgical mortality here reported has occurred in spite of the participation of a large number of inexperienced technicians, it can be considered due less to increasing technical skill than to the develop-

ment of measures for the protection of the surgical patient applied under the advice and direction of experienced surgeons. A progressive drop in mortality in a series of cases operated upon by an individual surgeon can be ascribed in part to increasing technical skill, but his increasing knowledge of disease and his adoption of improvements in general surgical care may play the major rôle. We would not deny that technical dexterity has a place in

surgical results, but we would present for consideration, as have Cushing, and others,⁸ the idea that it may be less important than other factors.

Finally, the urgency of repeatedly presenting surgical results to the profession at large must be considered. The success of surgery as a whole and the opportunities for surgery to accomplish the most good for the greatest number of sick people depends in considerable part upon its reputation among family doctors and consultants in internal medicine. Many of these practitioners base their judgment of surgical mortality on what they were taught during their surgical courses in medical school. They do not have ready access to surgical journals in which recent statistical data are usually published. It is the task of these men to give the primary advice leading to surgical consultation. Theirs is the first choice; and

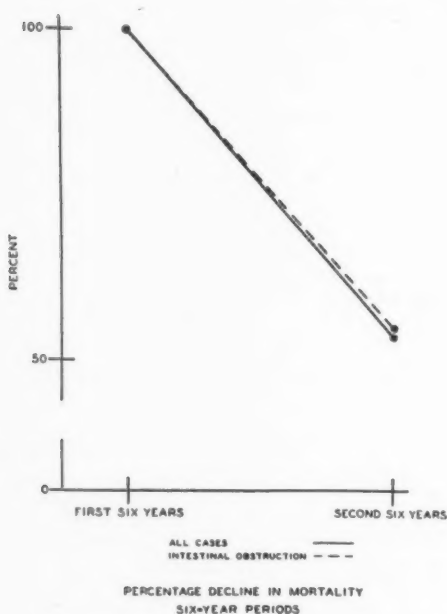


CHART 2.—Comparative percentage decline in mortality rate of all cases and of cases of intestinal obstruction in two six-year periods, 1934-1939 and 1940-1945, respectively.

it is quite natural that they will base that choice on their knowledge, no matter where or when derived, of surgical risk. Many conscientious practitioners, of course, familiarize themselves with modern surgical risk and give advice based on sound information, but many do not. There appears, therefore, to be some need for surgery to broadcast its accomplishments beyond its own sphere, not with boastful intent but for the purpose of bringing surgical relief to more people. If it were possible to present periodically between the covers of a single publication the surgical mortalities attained by a group of representative hospitals, the internist and the family doctor would have a ready source of reference for this information. Such a compilation would also furnish all surgeons, including those working under less favorable circumstances, a yardstick for their own accomplishments. We suggest that one of the surgical societies study methods of accomplishing this needed end.

MORTALITY OF SURGICAL DISEASE

REFERENCES

- ¹ Brunschwig, A.: Extending Surgery in Treatment of Cancer of Colon. *Surgical Clinics of North America*, **24**, 185-202, 1944.
- ² Lahey, F. H.: Total Gastrectomy, Splenectomy, Resection of Left Lobe of Liver, Omentumectomy, and Colectomy upon One Patient in One Operation. *ANNALS OF SURGERY*, **119**, 222-224, 1944.
- ³ David, V. C., and Gilchrist, R. K.: Extension of Border Line of Operability in Cancer of Rectum. *ANNALS OF SURGERY*, **115**, 566-573, 1942.
- ⁴ Brooks, B.: Surgery in Elderly Patients. *ANNALS OF SURGERY*, **105**, 481-495, 1937.
- ⁵ Balfour, D. C.: Factors of Significance in the Prognosis of Cancer of the Stomach. *ANNALS OF SURGERY*, **105**, 733-740, 1937.
- ⁶ Fine, J., Hurwitz, A., and Mark, J.: A Clinical Study of the Plasma Volume in Acute Intestinal Obstruction. *ANNALS OF SURGERY*, **112**, 546-556, 1940.
- ⁷ Fulton, J. F.: Harvey Cushing, A Biography. Page 352, Springfield, Illinois, 1946.
- ⁸ Cole, W. H.: Symposium on Abdominal Surgery—Introduction. *Surgical Clinics of North America*, **24**, 1-2, 1944.

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DISCUSSION.—DR. JOHN C. BURCH, Nashville, Tenn.: This is a timely subject. Doctor Lehman's data clearly reflect the great progress made in reducing surgical mortality. In my opinion this decrease is general in the better clinics. Many of us are slow to accept change; for them, this paper will prove a needed stimulus. For our medical colleagues who harbor exaggerated ideas concerning the risks of surgery, it should prove enlightening. They may even refer a few more patients in an earlier stage of their disease. For the medical educator, the inference is plain. Many of the things taught ten years ago are not the things emphasized today. Much new progress must be assimilated by the profession. It is clear that surgery is a field of continuing study. Unless this primary fact is emphasized as the foundation of all surgical training, our young surgeon will find himself in the ranks of those unwilling to accept change. From an experience with many recent graduates it is my opinion that much remains to be accomplished along these lines.

Doctor Lehman did not stress the equally great strides which have been made in decreasing morbidity and shortening convalescence. Great improvement in the handling of surgical cases has resulted from a better understanding of the physiology of bed rest. The results of early rising are truly phenomenal. In recently reviewing a series of about 1,400 hysterectomies performed over a period of years, a striking reduction in the number of cases of thrombophlebitis was noted. It is, of course, difficult to attribute this to any one cause, but early mobilization of the surgical patient has undoubtedly played a most important rôle.

PRIMARY PULMONARY MALIGNANCY TREATED BY RESECTION*

AN ANALYSIS OF 129 CASES

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DURING THE ALMOST 11-YEAR PERIOD beginning January 1, 1936, and ending December 1, 1946, there were observed in our private practice and on our service in Charity Hospital of Louisiana, at New Orleans, 360 patients with pulmonary malignancy, 129 of whom were submitted to pulmonary resection. Two hundred and sixty-one cases, in 113 of which resection was performed, occurred in private practice and 99, in 16 of which resection was done, at Charity Hospital. It is the purpose of this report to present an analysis of the 129 resected cases, including the follow-up observations made on all patients who survived surgery.

INCIDENCE

Recent literature on carcinoma of the lung has emphasized the apparently increasing incidence, and in previous publications we have considered this phase of the subject.^{15, 18, 19} On the basis of both reports in the literature and our own experience the statement is justified that carcinoma of the lung has become one of the most frequently encountered malignant neoplasms, and that the lung is now preceded only by the stomach as a primary site of cancer.

Comparative statistics from Charity Hospital of Louisiana, at New Orleans, bear out these conclusions. During the ten-year period ending January 1, 1946 (Chart 1) the yearly incidence of carcinoma of the stomach, while it showed transient increases and decreases, was substantially unchanged, whereas the incidence of carcinoma of the lung showed a general slight increase. The rate for Negroes was practically level during this period, although carcinoma of the stomach was considerably more frequent in this race, while the incidence of pulmonary malignancy among white patients showed a definite general increase. The data suggest that the racial distribution of the disease may be significant. During the period in question the ratio of colored to white admissions was about equal, but the incidence of carcinoma of the lung was approximately 2 to 1 in favor of the white race (Chart 2).

Only seven (5.4 per cent) of the 129 resections were done in Negro patients, but the small number is not significant. The white preponderance is

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

Incidence of Carcinoma of Lung and Stomach Based upon Admissions at Charity Hospital

Jan. 1, 1936 to Jan. 1, 1946

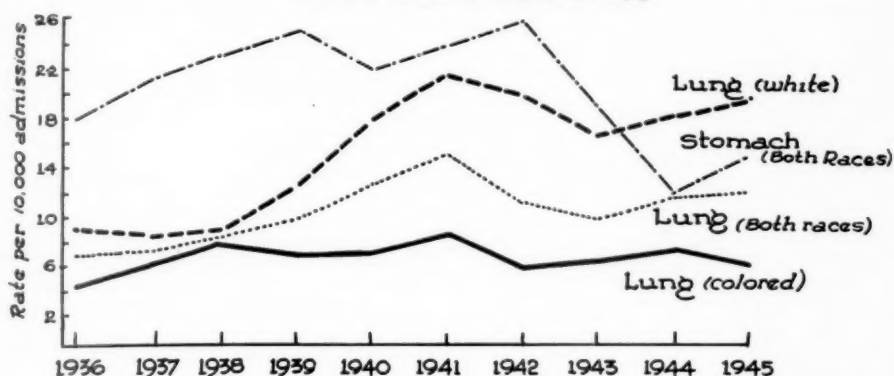


CHART 1.—Comparative incidence of carcinoma of the lung and stomach in the white and colored races based upon admissions at the Charity Hospital in New Orleans during the ten-year period, 1936–1945, inclusive.

Race Incidence of Carcinoma of Lung and Stomach Based on Admissions at Charity Hospital

Jan. 1, 1936 to Jan. 1, 1946

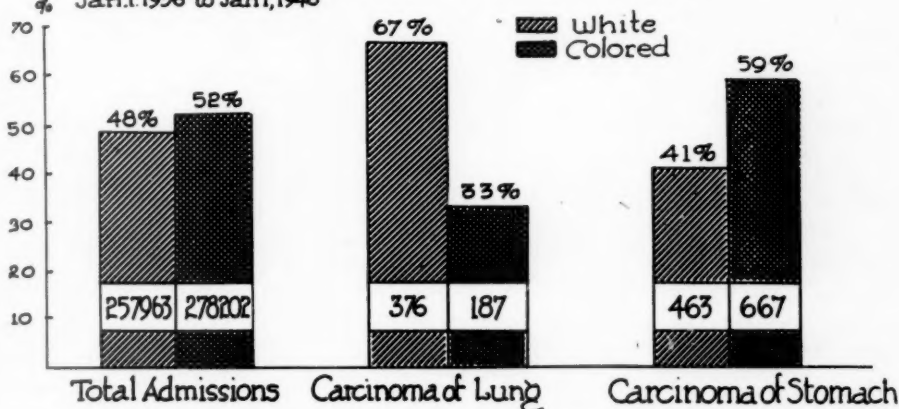


CHART 2.—Graphic representation of incidence of carcinoma of the lung and stomach in the white and colored races compared with total admissions of the two races in the Charity Hospital, New Orleans, Louisiana, during the ten-year period, 1936 to 1945, inclusive.

readily explained by the large proportion of cases treated at hospitals which serve only white patients.

Sex.—All experience indicates that carcinoma of the lung is predominantly a disease of males, though no satisfactory explanation for the sex discrepancy has been advanced. In the 360 clinical cases observed by us there

Pulmonary Malignancy treated by Resection
129 Cases

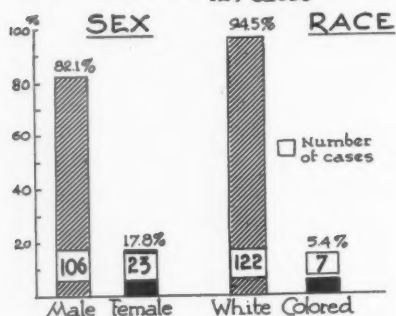


CHART 3.—Graphic representation of the sex and race incidence in the authors' series of 129 cases of pulmonary malignancy treated by resection.

were 311 males (86.3 per cent) and 40 females. Among the 129 resected cases there were 106 males (82.1 per cent) and 23 females (Chart 3). These figures are in line with the proportions found in 8,575 collected cases of carcinoma of the lung, in which 6,769 patients (78.9 per cent) were males and 1,806 females.¹⁵ If so-called mixed tumors (adenomas) are considered, the sex ratio is distinctly different, there being a small female preponderance in this type of growth.

Pulmonary Malignancy—Age Incidence

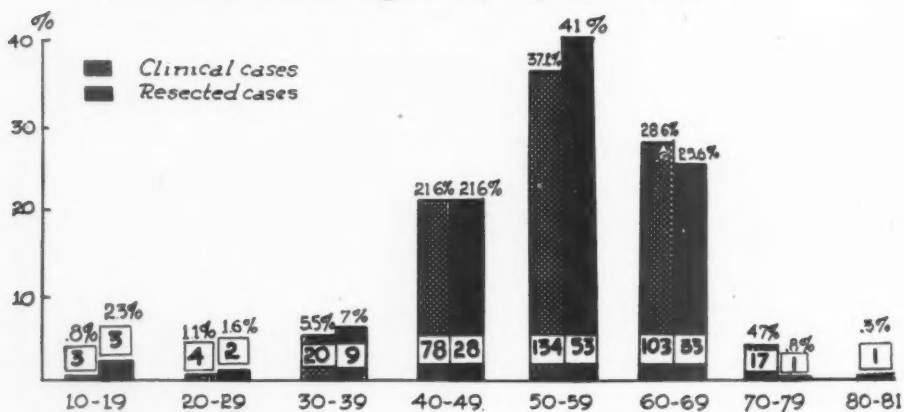


CHART 4.—Graphic representation of age-incidence by decades in the authors' series of 360 clinical and 129 resected cases of pulmonary malignancy.

Age.—It is the general experience that while carcinoma of the lung may occur at almost any period of life, it is most frequent in the 5th, 6th, and 7th decades. In our total series, as well as in our resected cases, almost 90 per cent of the patients were in this age-group (Chart 4).

PULMONARY MALIGNANCY

ETIOLOGY

The numerous explanations advanced to account for the apparent increase in incidence in carcinoma of the lung have been reviewed in previous publications and will not be discussed here.^{15, 18, 19} In the 129 resected cases no factor was found which might bear a significant relationship to the occurrence of the disease. Neither occupation nor smoking habits, which some reports, including our own, have stressed as of possible etiologic significance, seemed of any special significance in this particular series (Charts 5 and 6).

Pulmonary Malignancy treated by Resection
129 cases

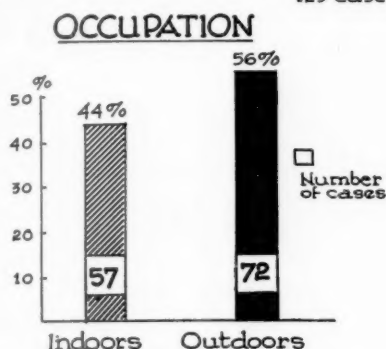


CHART 5.—Graphic representation of type of occupation in the authors' series of 129 cases of pulmonary malignancy treated by resection.

Pulmonary Malignancy Treated by Resection
129 cases

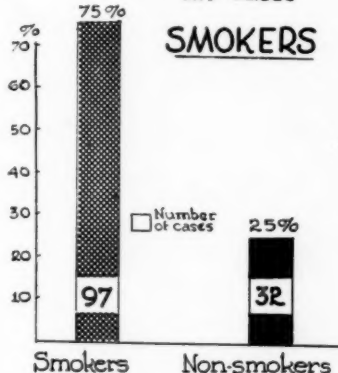


CHART 6.—Graphic representation of incidence of smokers and nonsmokers in the authors' series of 129 cases of pulmonary malignancy treated by resection.

PATHOLOGY

The pathologic picture in our series of cases of carcinoma of the lung will form the subject of another report, and will not be discussed at this time. It is important to note, however, that the 129 resected cases included 124 cases of bronchiogenic carcinoma, two cases of fibrosarcoma, and one case each of melanosarcoma, neurogenic sarcoma, and lymphoblastoma. In 76 cases the involvement was on the right side, and in 53 on the left (Chart 7), which is in correspondence with most of the reports in the literature. The greater frequency of occurrence on the right side possibly can be explained on the basis of the larger size of the right lung. The incidence of involvement in the upper lobe on each side and in the right lower lobe was practically the same (Chart 7).

CLINICAL PICTURE AND DIAGNOSTIC CONSIDERATIONS

The clinical picture of carcinoma of the lung is not sharply characteristic, and this fact, plus the usually insidious onset, undoubtedly explains the fre-

quent delay in diagnosis. An analysis of the 129 resected cases, which form the basis of this study, bears out other reports, and indicates that the most common symptoms are cough, loss of weight, discomfort or pain in the chest, and hemoptysis, in about that order of frequency (Chart 8). The next most frequent clinical manifestations, in addition to a history of previous respiratory infection, are dyspnea, wheezing, and changes in the voice (Chart 8).

This series also makes clear how important it is to remember that in many cases, and particularly in the earlier cases, not more than one or two complaints may be present. The paucity of symptoms accounts for the difficulty frequently encountered in framing a characteristic clinical picture in the early stages of the disease and makes it doubly important to bear constantly in mind the possibility of pulmonary malignancy in any patient over 40 years of age,

Pulmonary Malignancy Treated by Resection
SITES OF INVOLVEMENT

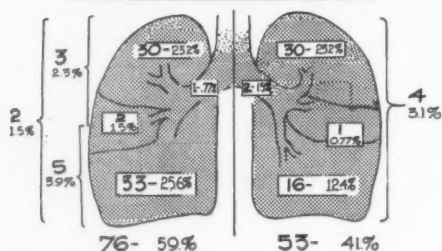


CHART 7.—Diagrammatic representation of incidence of sites of involvement in the authors' series of 129 cases of pulmonary malignancy treated by resection.

Pulmonary Malignancy treated by Resection
COMPARATIVE INCIDENCE of RECORDED SYMPTOMS

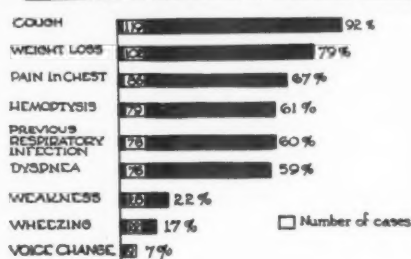


CHART 8.—Graphic representation of the incidence of recorded symptoms in the authors' series of 129 cases of pulmonary malignancy treated by resection.

particularly any male patient, with symptoms referable to the respiratory system. The recollection of the possibility is the key to improvement in the diagnosis of early cases.

The physical findings in carcinoma of the lung vary considerably and depend upon the site, size, and direction of growth of the tumor. Significant findings are more likely to be encountered if the tumor encroaches upon the lumen of the larger bronchi or upon the pleura. Generally speaking, the physical findings, like the symptoms, are not characteristic, and in early cases the examination is likely to be negative.

Roentgenology.—Of all diagnostic methods in carcinoma of the lung the most important is roentgenologic examination. It resulted in a positive diagnosis in 105 of our 129 resected cases, 81 per cent (Chart 9), which is in accordance with the 60 to 80 per cent of successful diagnoses reported by this method in the literature. The most frequent error, the diagnosis of lung abscess, was actually not usually an error, since in almost every case thus

PULMONARY MALIGNANCY

diagnosed an abscess was actually present in association with the pulmonary malignancy.

Bronchography (with lipiodol) is a very useful diagnostic procedure in certain types of cases, particularly those in which the tumor is not of sufficient size or density to cast a shadow on plain roentgenologic examination and in which the lesion is one of the small bronchi and, therefore, cannot be visualized by bronchoscopy.

It cannot be too strongly emphasized that carcinoma of the lung will continue to be overlooked until all physicians develop the habit of routine roentgenologic examination of all patients with any symptoms referable to the chest unless they are clearly due to some other cause. The practice should be routine even when physical findings are negative. In four cases in this series the growth was discovered because roentgenologic examination was part of the diagnostic routine. Despite the accidental discovery, and the fact that all growths could be resected, histologic study of the hilar nodes showed that metastasis had already occurred in three of the four patients.

Bronchoscopy and Biopsy.—The most reliable method of diagnosis in bronchogenic carcinoma is visualization of the tumor by bronchoscopy and examination of a biopsied specimen. According to the literature, which is borne out by our own experience, the method is accurate in from 60 to 80 per cent of all cases, the proportion of correct diagnoses varying with the location of the tumor. Fortunately, the majority of malignant tumors of the lung are in bronchial segments which can readily be visualized. Lesions in the upper lobe and in the peripheral portion of the lung are much less likely to be diagnosed by bronchoscopy, and sometimes cannot be diagnosed at all by this method.

Bronchoscopy was performed in 112 (87 per cent) of our 129 resected cases (Chart 10), in 68 of which (61 per cent) a biopsy specimen could be obtained. The specimen was positive in 55 (81 per cent) of the 68 cases.

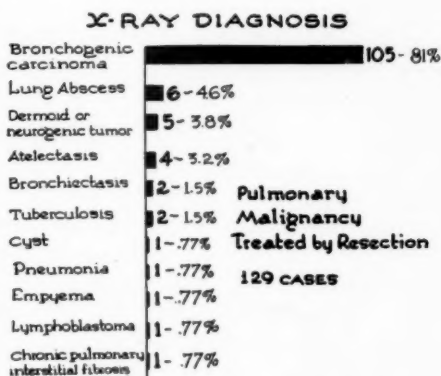


CHART 9.—Graphic representation of roentgenologic diagnoses made in the authors' series of 129 cases of pulmonary malignancy treated by resection.

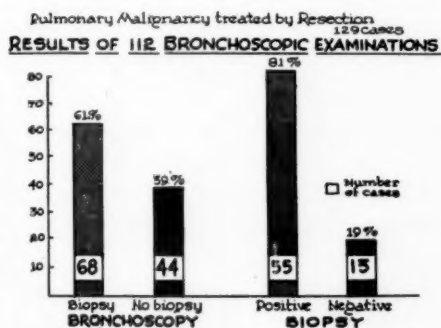


CHART 10.—Graphic representation of results of 112 bronchoscopic examinations performed in the authors' series of 129 cases of pulmonary malignancy.

Bronchoscopy was deliberately omitted in 17 of the 129 cases because roentgenoscopic examination revealed the growth to be so peripherally located that visualization by this means was obviously impossible.

Other Diagnostic Methods.—The microscopic examination of expectorated material or of material aspirated at bronchoscopy to determine the presence or absence of tumor cells is a diagnostic method of increasing importance which should be employed much more frequently than it is. It requires considerable experience, but in the hands of experienced observers it is of great value, particularly in cases in which bronchoscopic visualization of the tumor is not possible.

TABLE I
INCIDENCE OF OPERABILITY AND RESECTABILITY IN PRIMARY PULMONARY MALIGNANCY

Authors	Number of Cases Observed	Cases Explored		Cases Resected	
		No.	Per Cent	No.	Per Cent
Edwards.....1938	172	28	16.3	13	7.6
Churchill.....1940	156	52	33.3	27	17.3
Burnett.....1941	102	34	33.3	12	11.7
Fetter.....1943	31	6	19.3	0	0
Overholt.....1943	165	80	48.5	41	24.8
Brock.....1943-44	330	45	13.6	22	6.6
Clagett and Brindley.....1944	493	90	18.2	45	9.1
Rienhoff.....1944	...	181	39
Adams.....1946	157	94	59.8	49	31.2
Cames, Cesanelli, and Tricerri, 1946	107	21	19.6	12	11.2
Graham.....1946	221	112	50.7	39	17.6
Lindskog.....1946	100	32	32	12	12
Total.....	2,034	594*	29.2	272	13.4
Authors.....	360	210	58.3	129	35.8

* Actually this figure is probably somewhat higher, since it does not include a small proportion of cases in which operation was refused.

Aspiration biopsy is mentioned only to be condemned. The danger of implanting metastases in the pleura and chest wall is not merely theoretical. The implantation occurred in two of our own cases and has been reported by others.^{8, 17, 18} In our opinion the method is justifiable only in cases of suspected pulmonary malignancy which are obviously inoperable and in which an accurate diagnosis is of great importance.

If other methods fail, and if the diagnosis of carcinoma of the lung cannot positively be excluded, exploration of the chest should be regarded as part of the diagnostic procedure. When properly performed it is attended with a minimum mortality, and it frequently reveals an early, and, therefore, operable, growth. In our series of 210 cases in which exploration was done a positive diagnosis was established prior to operation in 146 (69.5 per cent).

OPERABILITY

The only satisfactory treatment of carcinoma of the lung is surgical extirpation of the involved area, preferably by pneumonectomy. Upon that point

PULMONARY MALIGNANCY

there is general agreement. Unfortunately, there is also general agreement that the incidence of operability is discouragingly low. Thus, it may be observed from Table I that in 2,034 cases of primary pulmonary malignancy collected from the literature, operation appeared feasible and exploration was done in 594 (29.2 per cent), but that resection actually was possible in only 272, or 13.4 per cent. While there are understandably considerable variations in the incidences of operability and resectability among these reported series, there is an encouraging trend toward higher incidences among the more recent reports. Our own experience (Charts 11 and 12) is in accord with these latter reports.

In the 360 cases of pulmonary malignancy diagnosed clinically, 109, or 30 per cent, were clearly inoperable. Of the 251 cases regarded as operable, surgery was refused by the patients in 41, or 10 per cent. Of the 210 cases explored, 81 proved inoperable, or 38.5 per cent, leaving 129 cases, or 35.8 per cent, of the whole group, in which resection could be done. What this amounts to is that of every three cases of clinical pulmonary malignancy only one eventually proves resectable. When it is recollected how many patients die after resection or, if they survive, die after discharge from the hospital, these figures are even worse than they seem.

Technical details have been discussed at length in previous communications,^{13, 14, 16, 18} and no attempt will be made to review them here. Pneumonectomy, as already mentioned, we consider the procedure of choice. It was performed in 127 of the 129 cases. Simple lobectomy was done in the other two cases, in one because at the time of operation the condition was thought to be inflammatory and in the other as a palliative procedure, to relieve the patient of severe and discomforting manifestations of an accompanying lung abscess.

Although both the anterior and the posterolateral approaches were employed, the anterior approach is preferred when it is not contraindicated. The posterolateral approach is chiefly used in cases in which it is believed that dense adhesions may be encountered, posteriorly and laterally.

In an effort to increase the limits of operability in the cases explored, certain supplementary procedures were carried out in some patients in whom the tumor had extended beyond the confines of the lung. For this reason ligation of the large hilar vessels was done within the pericardial cavity in 18 cases, resection and suture of a portion of the auricle in eight cases, resection of part of the diaphragm in seven cases, and resection of a portion of the chest wall in six cases (Chart 13).

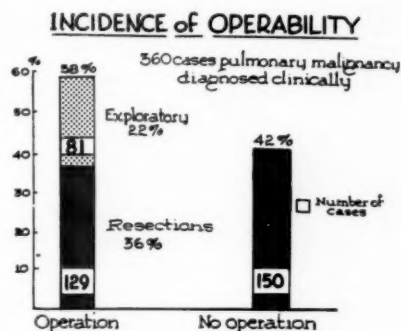


CHART 11.—Graphic representation of the incidence of operability in the authors' series of 360 cases of pulmonary malignancy.

POSTOPERATIVE MORBIDITY AND MORTALITY

Postoperative infection, in the form of empyema, occurred in 15 of the 129 cases, or 11.6 per cent. In five instances, or 3.8 per cent, the infection was the result of a blown bronchus (Chart 14). Only one of the five patients in this

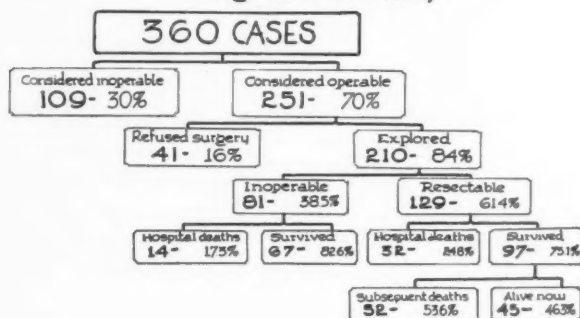
Results in 360 Cases of Pulmonary Malignancy
Diagnosed Clinically

CHART 12.—Schematic representation of the results in the authors' series of 360 clinical cases of pulmonary malignancy.

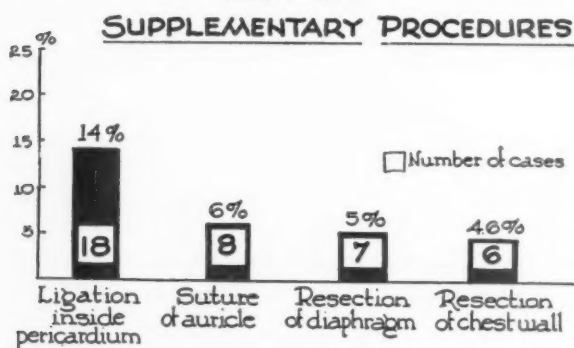
Pulmonary Malignancy Treated by Resection
129 CASES

CHART 13.—Graphic representation of supplementary procedures performed in the authors' series of 129 cases of pulmonary malignancy treated by resection.

group survived. Our experience with chemotherapy, whether in the form of sulfonamide drugs or penicillin, has not been very encouraging, and it is our general impression that the introduction of these agents has not materially influenced the incidence of the morbidity of this complication.

PULMONARY MALIGNANCY

Of the 129 patients in whom resection was done, 32, or 24.8 per cent, died in hospital (Chart 15). Cardiovascular complications (Chart 16) were responsible for 15 deaths, almost half of the total number, and respiratory infections, especially pneumonia, for the next largest number. In the remaining eight deaths the cause of the fatality was hemorrhage in four, and these

Pulmonary Malignancy Treated by Resection
129 CASES

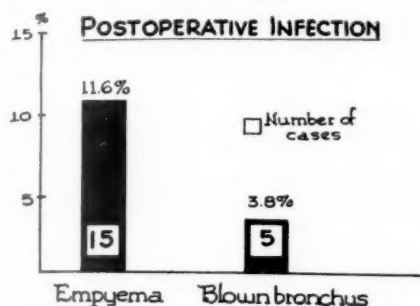


CHART 14.—Graphic representation of incidence of postoperative infection in the authors' series of 129 cases of pulmonary malignancy treated by resection.

HOSPITAL MORTALITY IN 129 CASES

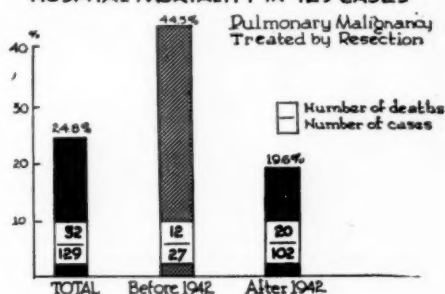


CHART 15.—Graphic representation of hospital mortality in authors' series of 129 cases of pulmonary malignancy treated by resection.

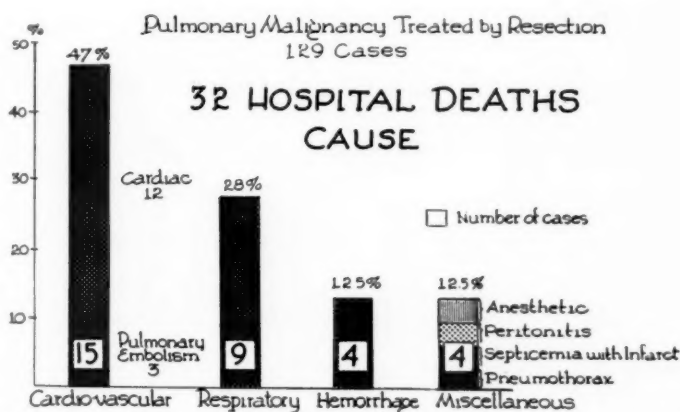


CHART 16.—Graphic representation of cause of hospital deaths in authors' series of 32 cases of pulmonary malignancy.

fatalities, as well as those due to anesthetic causes and to pneumothorax, may be classified as due to technical errors and, therefore, preventable. The relatively high incidence of cardiovascular complications, however, is for the most part not preventable. They represent a risk which must be assumed in pneumonectomy for carcinoma of the lung unless the criteria of operability are

so strictly limited that patients in whom they are likely to occur are excluded from surgery and are, thus, denied their only chance of salvage.

The largest number of hospital deaths, 12, or 37.5 per cent, occurred within 24 hours of operation (Chart 17). Seven others occurred before the 5th day, or 22 per cent, seven before the 10th day, or 22 per cent, four before the 15th day, or 12.5 per cent, and one each on the 18th and 43rd day, respectively.

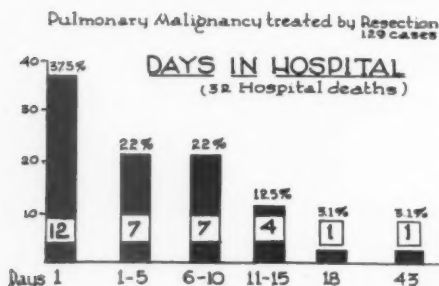


CHART 17.—Graphic representation of postoperative survival period of 32 hospital deaths in authors' series of pulmonary malignancy treated by resection.

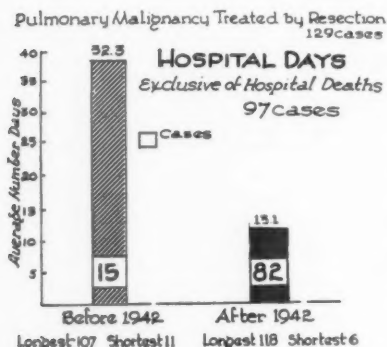


CHART 18.—Graphic representation of period of hospitalization (exclusive of hospital deaths) in the authors' series of pulmonary malignancy treated by resection, according to whether operation was performed before or after 1942.

The major portion of the immediate postoperative mortality, thus, occurred within the first ten days, and approximately half of the deaths in this group occurred within the first 24 hours after operation, usually from cardiovascular causes (Chart 17).

When the resected cases are divided into those which were operated upon before January 1, 1942, and those which were operated upon after that date, it is apparent that the hospital mortality in the former group is 44.5 per cent and in the latter group 19.6 per cent (Chart 15). It is fair to assume that the reduction is attributable to improvement in technic, as well as preoperative and postoperative care. Among the patients who survived operation, the postoperative hospital stay days prior to 1942 averaged 32.3, and after that date 13.1. The shortened period of hospitalization in the second period is also a reflection of the improvements mentioned (Chart 18).

FOLLOW-UP OBSERVATIONS

Every patient in this series who was submitted to operation six months, or more, ago and who left the hospital alive has been followed up to date, the examination in the great majority of cases being made personally by one

of us. At this time, our report concerns only the absolute survival rates, without reference to the presence or absence of recurrence at the last examination or to any other factor which might conceivably influence the patient's chances for survival.

It seems scarcely necessary to point out that because the 107 patients involved in these calculations were operated upon at varying periods of time over the past ten years, the number of cases in each time-category is different, and that the numbers become smaller as the possible survival-time increases.

PULMONARY MALIGNANCY

Patients operated upon only a year ago, for instance, obviously have had no opportunity to survive longer than a year. Incidentally, it would be very desirable if surgeons who have series of lobectomies to report should calculate

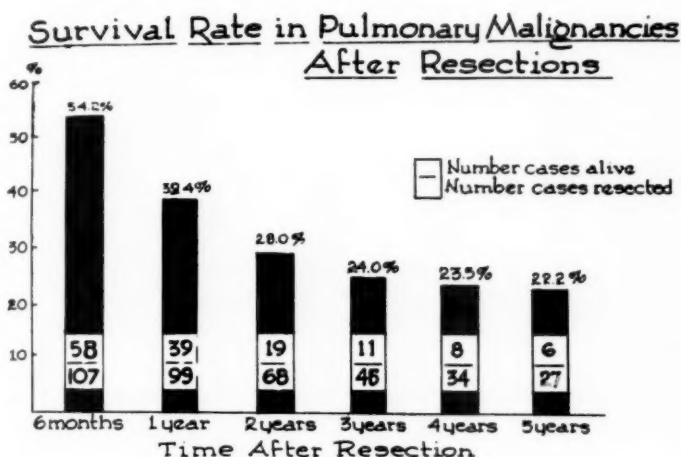


CHART 19.—Graphic representation of survival rate after resection in authors' series of pulmonary malignancy.

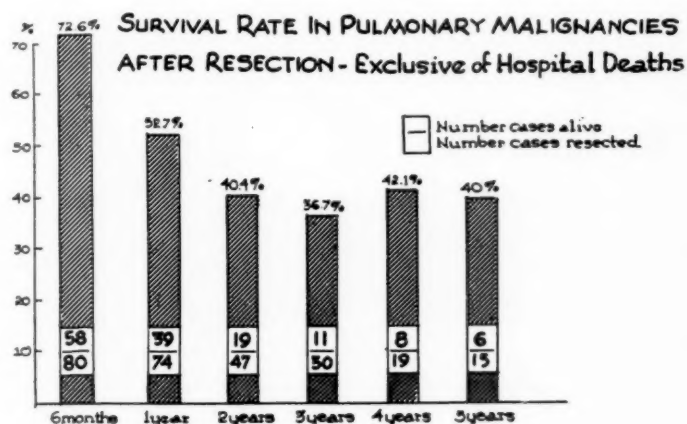


CHART 20.—Graphic representation of survival rate after resection, exclusive of hospital deaths in authors' series of pulmonary malignancy.

the survival-times on the basis of the studies reported herewith, so that the relative merits of the two procedures might be evaluated on the most essential of all criteria, how long the patient lives.

Gross Survival Rate.—Of the 107 patients operated upon six months, or more, ago (Chart 19), only a little over half (58) survived the first six-month period after operation. The 49 deaths within this period, however, include 27

SURVIVAL RATES IN PULMONARY MALIGNANCIES AFTER RESECTION
According to Extension and Localization of Lesion

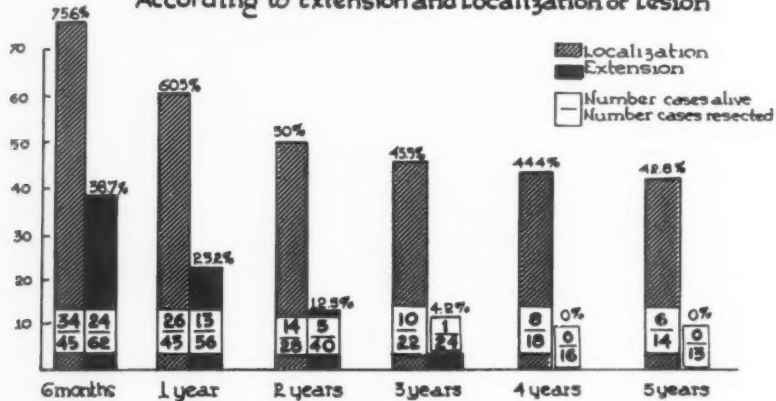


CHART 21.—Graphic representation of survival rate after resection according to extension and localization of lesion in authors' series of pulmonary malignancy.

SURVIVAL RATES IN PULMONARY MALIGNANCIES AFTER RESECTION
EXCLUSIVE OF HOSPITAL DEATHS
According to localization and Extension

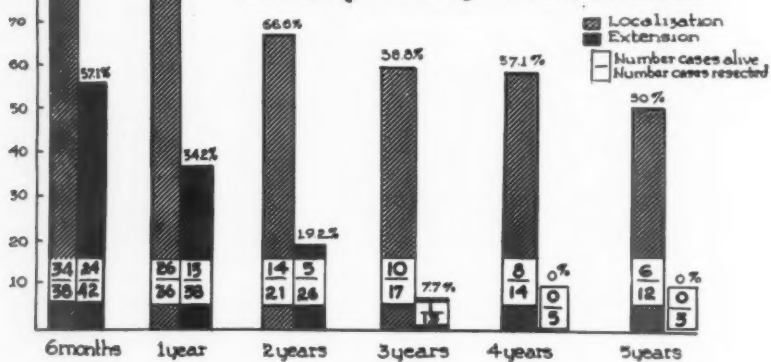


CHART 22.—Graphic representation of survival rate after resection exclusive of hospital deaths according to localization and extension of lesion in authors' series of pulmonary malignancy.

deaths which occurred in the hospital immediately after operation. Approximately three-fifths of the patients, again including those who died in the hospital, died within the first year. After that time, however, the rate of death increases very much less rapidly, and by the end of five years approximately

PULMONARY MALIGNANCY

a fifth of all the patients submitted to resection were still alive. To express it differently, the distribution curve for the survival rate drops rather rapidly within the first year after operation, but by the third year has been stabilized and continues almost as a plateau until the fifth year. The assumption seems reasonable that a patient who lives through the third year after operation has a good chance of being alive at the end of five years. At the present time three patients are alive in the fifth year after operation and one each in the sixth and the tenth year after operation.

When the survival rate is calculated on the basis of the patients who left the hospital alive after surgery, those who died in hospital being excluded (Chart 20), the distribution curve is similar to the curve just described but is

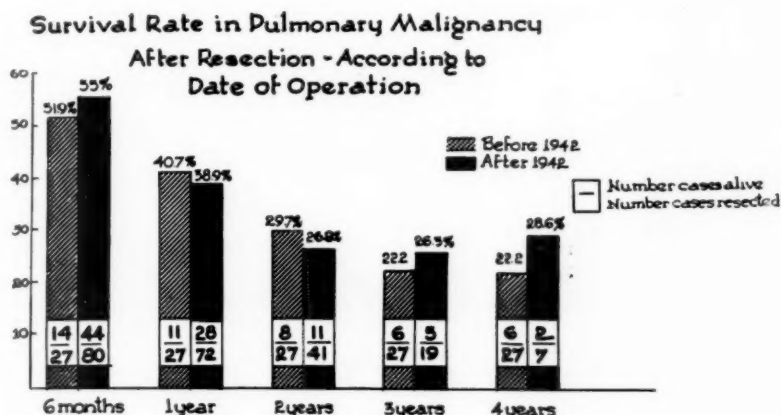


CHART 23.—Graphic representation of survival rate after resection according to date of operation in authors' series of pulmonary malignancy.

considerably more encouraging, the survival rate at the end of five years reaching 40 per cent, against 22 per cent when all patients are included.

Survival Rate According to Status of Growth.—Of all the factors which might affect the survival rate in carcinoma of the lung the most obvious is the status of the growth, as determined at operation and by pathologic study of the resected specimen. The 107 cases in which operation was performed six months, or more, ago were, therefore, analyzed from the standpoint of whether the growth was limited to the lung or had extended beyond it by encroachment upon contiguous structures or by regional metastases (Chart 21). As might have been expected, the survival rate was significantly greater among the patients whose growths were localized, no patient with extension at operation surviving beyond the three-year period, whereas the survival rate among patients with localized growths was 42.8 per cent at the end of five years. The curve is substantially the same when it is calculated on the basis of only the patients who left the hospital alive (Chart 22), the survival rate

among these patients with localized growths being 50 per cent at the end of five years.

Survival Rate in Relation to Date of Operation.—As already noted (Chart 15), the hospital mortality of pulmonary resection for carcinoma of the lung showed a distinct improvement after 1942, as compared with the mortality prior to that period, the improvement being attributed to improvements in technic and in preoperative and postoperative care. In an effort to determine whether the survival rate reflected the same improvement when analyzed

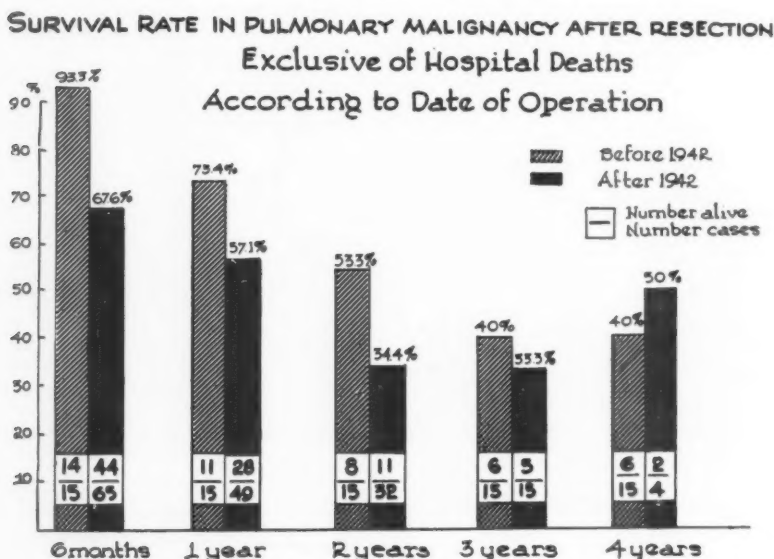


CHART 24.—Graphic representation of survival rate after resection, exclusive of hospital deaths, according to date of operation in authors' series of pulmonary malignancy.

according to the time at which operation was performed, the localized and nonlocalized cases were considered from this standpoint. When the group is analyzed as a whole (Chart 23), no significant differences are noted in the rates of survival before and after 1942. Even when the deaths in hospital are excluded (Chart 24), no great differences are observed. When the material is divided into localized (Chart 25) and nonlocalized (Chart 26) cases, the differences already commented upon in survival rates are once more apparent. In addition, there is small improvement in the survival rates for patients with nonlocalized growths after 1942, which perhaps reflects the better care, technically and otherwise, all patients received after that date.

No matter how the calculations are made, it is evident that the patient with a localized growth has, as, of course, might be expected, a much better chance of surviving for a considerable period of time after operation than has the patient with a nonlocalized growth. His chances are naturally influenced

PULMONARY MALIGNANCY

by the type of care he receives, but the important consideration is that he is seen early, so that complete removal of the lesion is possible and can be achieved without undue risk at operation.

Actual and Possible Survival Rates.—The analysis of this series of 129 cases of carcinoma of the lung in which resection was done is discouraging from the standpoint of absolute figures. Five years after operation 21 of the 27 patients operated upon, who could have survived this period of time, had died. The figures are less discouraging, however, when it is recalled that without operation all of them would inevitably have died, and that all of them would have been denied the longer or shorter period of postoperative health

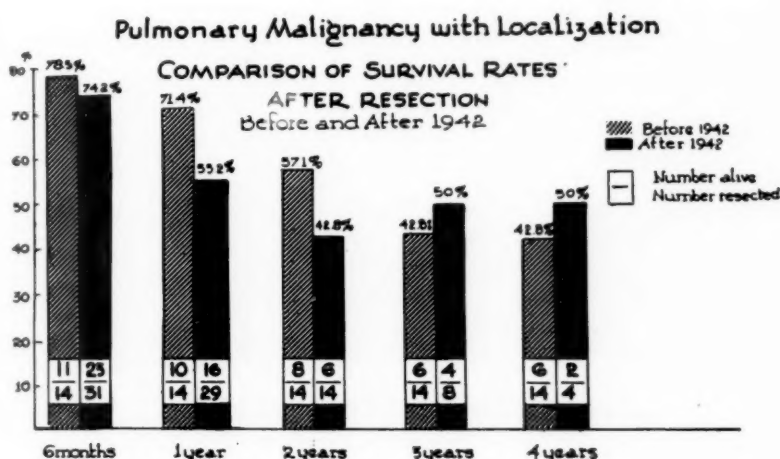


CHART 25.—Graphic representation of survival rate after resection according to date of operation in authors' series of pulmonary malignancy with localized lesion.

which many of those who eventually died did enjoy. Furthermore, the analysis of this series of cases clearly indicates what can be achieved in favorable cases, that is, the patients who are seen early enough to permit resection of the growth. At the present time (Chart 27), of every 25 clinical cases of carcinoma of the lung only nine are resectable, and of those nine, only two patients survive five years, or more. If every patient could be seen early enough to permit resection—a difficult but not necessarily an impossible goal—between five and six would survive five years, or more. There is no good reason why we should not at least set our sights to achieve such a result.

SUMMARY AND CONCLUSIONS

During the almost 11-year period ending December 1, 1946, 360 patients with carcinoma of the lung were observed, of whom 129 were submitted to pulmonary resection. The 129 resected cases are analyzed from the various standpoints, with special emphasis on diagnostic considerations and on sur-

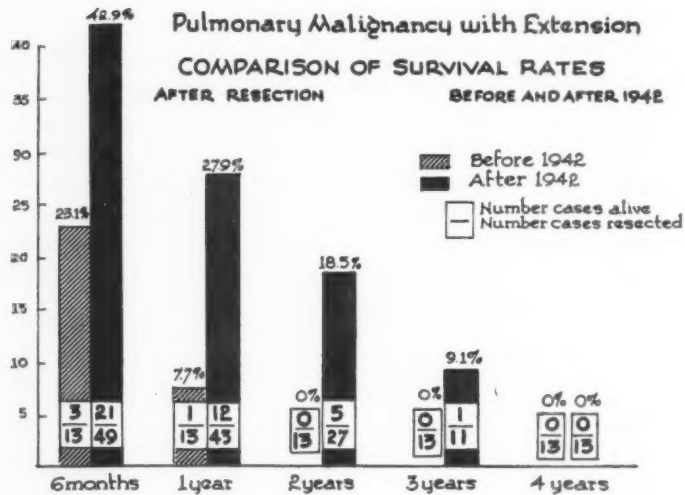


CHART 26.—Graphic representation of survival rate after resection according to date of operation in authors' series of pulmonary malignancy with extension of lesion.

SURVIVAL EXPECTANCY IN PULMONARY MALIGNANCY

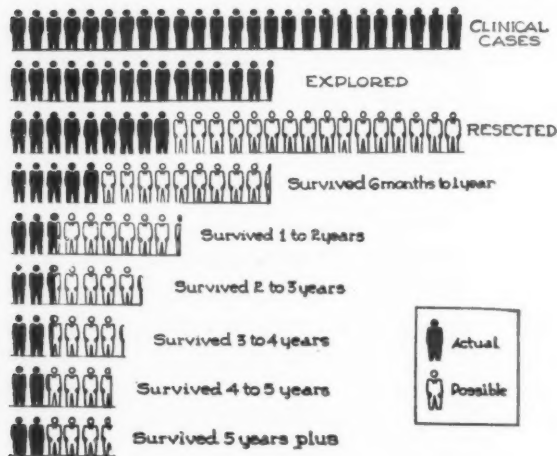


CHART 27.—Schematic representation of actual survival expectancy in pulmonary malignancy based upon present experience (in black) and of possible survival expectancy if all cases were diagnosed early enough to permit resection.

PULMONARY MALIGNANCY

vival rates. In most respects the data in this series bears out the data reported by other observers.

The key to early diagnosis is the recollection of the possibility of the disease in all patients with symptoms referable to the chest, particularly those over 40 years of age. Routine roentgenologic examination is the most valuable of all diagnostic methods. It should be supplemented as indicated by bronchography, bronchoscopy and biopsy, aspiration of expectorated material or of material aspirated at bronchoscopy, and, if the diagnosis cannot otherwise be arrived at, by exploratory thoracotomy.

The incidence of operability in carcinoma of the lung remains discouragingly low. The surgical mortality has shown progressive improvement and is not high if it is remembered that the mortality of the disease in the absence of operation is 100 per cent.

The immediate surgical mortality is caused by a certain proportion of preventable errors, but the incidence of cardiovascular complications, which are not usually preventable, is high, and the risk must be assumed if patients likely to develop them are not denied their chance of salvage.

An analysis of all patients in the series operated upon six months, or more, ago indicates that a patient who lives through the third year after operation has a good chance of being alive at the end of five years. The survival rate is significantly greater in patients whose growth was localized, no patient with extension at operation having survived beyond the three-year period. Every calculation, regardless of the standpoint from which it is made, indicates that while the patient's chances of survival are influenced by the type of care he receives, the important consideration is that he is seen early, so that complete removal of his lesion is possible and can be achieved without undue risk at operation.

REFERENCES

- ¹ Adams, Ralph: Primary Lung Tumors. *J. A. M. A.*, **130**, 547-553, March 2, 1946.
- ² Brock, R. C.: Surgical Treatment of Bronchial Carcinoma. *Brit. M. J.*, **2**, 257-259, August 28, 1943.
- ³ Brock, R. C.: Carcinoma of the Lung. *Brit. J. of Radiology*, **17**, 102-105, 1944.
- ⁴ Burnett, W. E.: Discussion of article by Gebauer, P.: Differentiation of Bronchiogenic Carcinomas. *J. Thoracic Surg.*, **10**, 395, 1940-41.
- ⁵ Cames, Oscar J., Cesanelli, Alfredo, and Tricerri, Fernando E.: Clinical Experience in the Surgical Treatment of Cancer of the Lung. *La Prensa Medica Argentina*, **33**, 1621, August 9, 1946.
- ⁶ Churchill, Edward D.: Resection of the Lung, *Surgery*, **8**, 961-991, 1940.
- ⁷ Clagett, O. Theron, and Brindley, G. V. Jr.: Bronchogenic Carcinoma. *Surg. Clin. of N. Amer.*, pp. 839-849, August, 1944.
- ⁸ Dolley, F. S., and Jones, J. C.: Lobectomy and Pneumonectomy for Lung Suppuration and Malignancy. *Journal-Lancet*, **59**, 162, 268, 1939.
- ⁹ Edwards, Tudor: Carcinoma of the Bronchus, XIeme Congres de la Societe Internat. de Chirurgie, **2**, 529-534, Bruxelles, 1938.
- ¹⁰ Fetter, Ferdinand: Carcinoma of the Lung: A Review of 31 Proved Cases at the Philadelphia Naval Hospital. *Ann. Int. Med.*, **18**, 978-987, 1943.
- ¹¹ Graham, Evarts A.: Discussion of article by Lindskog: Bronchiogenic Carcinoma. *ANNALS OF SURGERY*, **124**, 672, October, 1946.

- ¹² Lindskog, Gustaf E.: Bronchiogenic Carcinoma. *ANNALS OF SURGERY*, **124**, 667-672, October, 1946.
- ¹³ Ochsner, Alton and DeBakey, Michael E.: Primary Pulmonary Malignancy: Treatment by Total Pneumonectomy: Analysis of 79 Collected Cases and Presentation of Seven Personal Cases. *Surg., Gynec., and Obstet.*, **68**, 435-451, February 15, 1939.
- ¹⁴ Ochsner, Alton and DeBakey, Michael: Surgical Considerations of Primary Carcinoma of the Lung: Review of the Literature and Report of 19 Cases. *Surgery*, **8**, 992-1023, December, 1940.
- ¹⁵ Ochsner, Alton, and DeBakey, Michael: Carcinoma of the Lung. *Arch. of Surg.*, **42**, 209-258, February, 1941.
- ¹⁶ Ochsner, Alton and DeBakey, Michael: Carcinoma of the Lung. *N. O. Med. and Surg. J.*, **93**, 387, 1941.
- ¹⁷ Ochsner, Alton and DeBakey, Michael: Significance of Metastasis in Primary Carcinoma of the Lung. *J. Thoracic Surg.*, **11**, 357-387, April, 1942.
- ¹⁸ Ochsner, Alton, Dixon, J. Leonard, and DeBakey, Michael: Primary Bronchiogenic Carcinoma: An Analysis of 190 Cases, 58 of which were Successfully Treated by Pneumonectomy: A Review of the Literature. *Clinics*, **3**, 1187-1245, 1945.
- ¹⁹ Ochsner, Alton, Dixon, J. L., and DeBakey, Michael: Primary Bronchiogenic Carcinoma. *Dis. of the Chest*, **11**, 3, 1945.
- ²⁰ Overholt, Richard H.: A Common Masquerading Lung Disease. *Dis. of the Chest*, **9**, 197-211, May-June, 1943.
- ²¹ Rienhoff, William F.: The Present Status of the Surgical Treatment of Primary Carcinoma of the Lung. *J. A. M. A.*, **126**, 1123-1128, December 30, 1944.

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THE PRESENT STATUS OF THE SURGICAL TREATMENT OF CARCINOMA OF THE LUNG*

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THIRTEEN YEARS have now elapsed since the first total pneumonectomy was performed in the Johns Hopkins Hospital. Previous to that time a diagnosis of pulmonary malignancy was made infrequently and more for academic than practical reasons. Prior to this time no therapeutic measures or methods were available which offered the patient more than palliation. Medicinal and radiation therapy were then, as now, equally ineffective and the disease when so treated was, and is, always fatal.

The surgical treatment of malignant tumors of the lung has been a boon to patients and a lively stimulus to clinicians interested in pulmonary lesions. Because of this increased interest on the part of physicians the diagnosis of tumors of the lung is made much more frequently than in the past, with the result that a greater number of such patients are being referred for operation. In a Medical Center in which a special interest in this type of surgery has been manifested, what seems a disproportionate increase in the frequency of these cases is apt to occur, but it may probably be true that the incidence of primary pulmonary cancer is on the increase.

It is the purpose of this report to record the clinical analysis, preoperative preparation, operative procedure, immediate and remote postoperative results in a series of 327 consecutive cases of carcinoma of the lung which have been referred for surgical treatment, not accounting for those instances in which the patient was obviously inoperable from the standpoint of the clinical findings.

CLINICAL ANALYSIS

Etiology.—Although the etiologic factors involved in the production of cancer are unknown, there is enough data accumulated to draw some conclusion as to the influence of certain factors to which human beings are exposed. In this and other series of cases reported, one fact has been outstanding as probably playing a definite rôle in the production of pulmonary carcinoma, that is the great majority of patients afflicted with this malady are residents of urban districts. In such districts, from the cradle to the grave, the lungs are constantly exposed to many irritating substances, such as dust, dirt, various fumes, gases and other atmospheric pollutions which have a deleterious effect on the lining cells of the bronchial tree throughout its entire extent. It is a well-known fact that miners and, particularly in various places in the world,

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laborers exposed to certain foreign particles in the air, are very prone to develop growths in the lung. It is also fully recognized that individuals who are working in contact with irritating gases, such as chlorine and others, frequently develop epithelial growths in the air passages. Changes in oxygen tension will affect the type of epithelial lining cells, often causing a metaplasia from the cylindrical cell to a flat cell. This morphologic transposition may also be found in the bronchi which are tributaries to areas of infection, such as lung abscess or bronchiectasis. In other words, chronic irritation, regardless of the type, will produce changes in the growth-rate and shape of the cells of the lung which seem to be very sensitive to this pollution of the atmosphere. It will be interesting, now that women are smoking, to see if the much higher ratio of the malignancy of the lung in men, is decreased by an increase in the incidence in women.

Due to the occupational hazards mentioned above as well as habits, a higher incidence of primary malignant tumors of the lung is to be expected in the male than in the female. Table I shows the distribution according to sex of the patients in this series. It is to be noted that there is a much higher incidence in the male than in the female, a ratio of almost 6 to 1 in favor of the males. The incidence of involvement of the right and left sides is approximately the same.

In regard to the age incidence of primary malignant tumors of the lung, this does not vary to any great extent from the age incidence of malignant growths elsewhere in the body. The majority of the patients were in the fourth to sixth decades. Perhaps patients in the second to fourth decades were more frequently affected than would be the case of other viscera; however, this series of cases, although relatively large, is far too small to warrant an exact statement. Twelve of the cases fall into the sixth decade. The oldest patient in this series to be operated upon was 76 years of age and the youngest 19. Age, in itself, seems to offer no contraindication to operation. Not infrequently an older patient from a physiologic point of view is a far better operative risk than a younger one. In this series the older patients were surprisingly unaffected by the operative procedure, including the patient age 76, and generally had uneventful postoperative convalescences. Pulmonary cancer, however, generally speaking, is a disease of advanced age.

Unfortunately for the lay public, physicians as a whole, because of the lack of therapeutic measures to combat such lesions or to effectively treat them, have been less acutely interested in the possibility of malignant growths of the lung than those of other viscera or organs of the body. It is, therefore, important that not only all physicians, but also the lay public, should become cognizant of their respiratory tracts in order that they may at the earliest moment seek confirmation or dissipation of their apprehensions in regard to signs and symptoms originating in their respiratory organs.

It is mandatory that the knowledge of the signs and symptoms originating as a result of malignant tumors of the lung be made known to the public as a whole, just as every woman knows the significance of a tumor of the breast

CARCINOMA OF LUNG

and realizes the importance of immediately consulting a physician concerning such a tumor.

In the analysis of this series of patients herein reported, in regard to the most frequent signs and symptoms occurring in such cases of primary cancer of the lung, only those signs and symptoms were included that could be attributed to involvement of the lung itself and not to invasion of contiguous structures or distant metastases. In 71 per cent of the patients in this series cough was the chief symptom. In a nation of heavy cigarette smokers, in which the population supplying the majority of patients breathes the polluted atmosphere of cities, cough is almost universal and is due mainly to nonspecific irritation of the respiratory tract. The important point about coughing that should make one suspicious of the presence of an intrabronchial growth is the departure from the normal for any individual. If in an adult "chronic cough"

TABLE I
DISTRIBUTION ACCORDING TO SEX OF CASES OF
PRIMARY CARCINOMA OF THE LUNG

	Operable	Inoperable
Male.....	84%	86%
Female.....	16%	14%

TABLE II
SIGNS AND SYMPTOMS OF CARCINOMA OF THE LUNG

Cough.....	71%
Hemoptysis.....	63%
Pain.....	50%
Loss of weight.....	39%
Hyperpnea.....	23%
Pneumonitis.....	18%
Fever.....	13%
Tightness in chest.....	3%

the type of cough changes to a spasmodic, productive or nocturnal type, or, again, if a person who has heretofore coughed infrequently suddenly begins to be annoyed by a hacking cough day and night, attention should be focused on the bronchial tree and the presence of a bronchial neoplasm should be suspected. The development of a cough or changes in the character of coughing can portend an extremely serious condition. Until physicians as a whole, as well as the lay public, become more acutely aware of the serious significance of this sign, the opportunity for early and satisfactory treatment of pulmonary neoplasms will be denied to many patients. It is to be noted, again, that the outcome in this condition, unless recourse is had to surgery, is invariably fatal. These symptoms and signs are listed according to the frequency of their occurrence in Table II.

In 63 per cent of our patients expectoration of blood or hemoptysis was associated with coughing. This varied from streaking of the sputum to the

expectoration of large and copious amounts of blood, up to six ounces (180 cc.). In the latter group the accumulation of blood in the mouth was preceded by a "gurgling" in the chest on one side which warned the patient of the impending hemoptysis. In our experience, copious hemoptysis has usually been associated with the adenocarcinoma type of intrabronchial growth. Unless

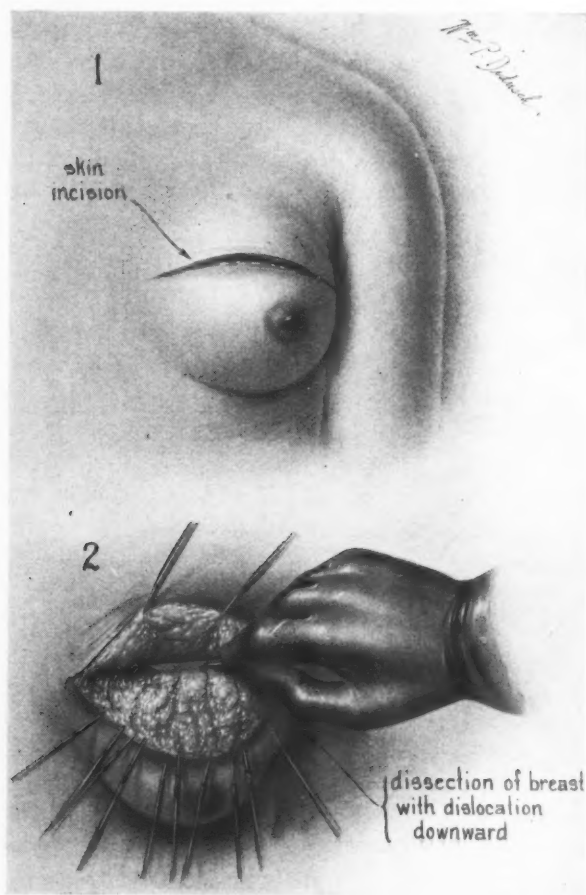


FIG. 1.—Demonstrating the first two operative steps using the anterior approach.

the roentgenograms and sputum examination are indisputably those of tuberculosis or bronchiectasis, hemoptysis must be considered to be due to an intrabronchial growth until this has been ruled out by the many types of examinations at our command. The burden of proof is on the physician who, in any given case, states that hemoptysis is not due to a tumor of the lung. This is true even though a small number of tubercle bacilli may be present in the sputum. Tuberculosis and cancer may be associated, and were in four cases

CARCINOMA OF LUNG

in our series. Clinical examinations to diagnose an intrabronchial tumor in no way interfere with the treatment of pulmonary tuberculosis; but if a patient bleeding from a tumor of the lung is observed for months in an attempt to prove the case to be tuberculosis, in many instances he will have lost his only opportunity for successful treatment. The discovery that the bleeding was originally from a neoplasm will have come too late.

Although it is uncommon to have pain as a prominent symptom in cancer of other organs, it is third in prominence among the signs and symptoms in patients afflicted with cancer of the lung. Pain arising from an intrabronchial neoplasm must be differentiated from the pain due to direct invasion of contiguous structures. Pain arising from the lung itself is not associated with the respiratory cycle, as is the pain of pleuritis. It is most often described by the patient as a constant dull ache deep in the chest. The frequency with which the actual position of the tumor, as shown by roentgenography, coincided with the location of the level of pain on the chest wall, as indicated by the patient, was surprising. In all probability pain does not arise within the tumor itself but is a result of pressure on the bronchial wall. Persistent pain in the chest, in the absence of inflammatory disease or aspiration of a foreign body, should always lead to careful investigation of the respiratory tract. Pain down the arm or in the chest wall, so characteristically found in the so-called "superior sulcus or Pancoast tumor," is, as a rule, due to direct invasion of the ribs or the brachial plexus or both. This distribution of pain is considered a very unfavorable symptom from the standpoint of operability.

Loss of weight due to cachexia in advanced carcinoma of any organ in the body, particularly the gastro-intestinal tract, is well-known and obvious; but not so easily understood was a striking loss of weight in 39 per cent of the cases of pulmonary carcinoma. This loss of weight was, of course, due in part to coughing, loss of appetite because of hemoptysis and sputum, worry, *etc.*; but the rapid gain of 30 to 50 pounds in a few months after total pneumonectomy for the removal of a relatively small growth remains unexplained.

Fifth on the list of signs and symptoms is hyperpnea, occurring in 23 per cent of the patients. These patients complained of a sudden desire to breathe in deeper breaths, not exactly similar to air hunger but approximating this condition. The deep breathing sensation one experiences when breathing carbon dioxide would seem to be similar. This paroxysmal hyperpnea came on suddenly and lasted for a few seconds or a few hours. The mechanism for this respiratory phenomenon is difficult to explain. It may possibly be caused by a plug of mucus occluding a secondary or tertiary bronchus already partly plugged by an intrabronchial neoplasm, the bronchopulmonary segment of lung, to which the occluded bronchus is a tributary, thus, becoming the site of an obstructive emphysema. Reflex disturbances in the respiratory rate and amplitude are thus set up. With expulsion of the mucus plug the respiratory rate returns to normal. Such unusual changes in the respiratory cycle, even though of short duration, should excite one's curiosity sufficiently to suggest a thorough examination of the bronchial tree.

Eighteen per cent of the patients had suffered from attacks of pneumonitis associated with episodes of fever and all the signs and symptoms characteristic of pneumonia. It was frequently possible to obtain a history of numerous attacks of so-called "pneumonia" in the recent past. The chief characteristic of these attacks was that they occurred at any time of the year, with apparently no tendency toward seasonal incidence, as in the true epidemic pneumonia.

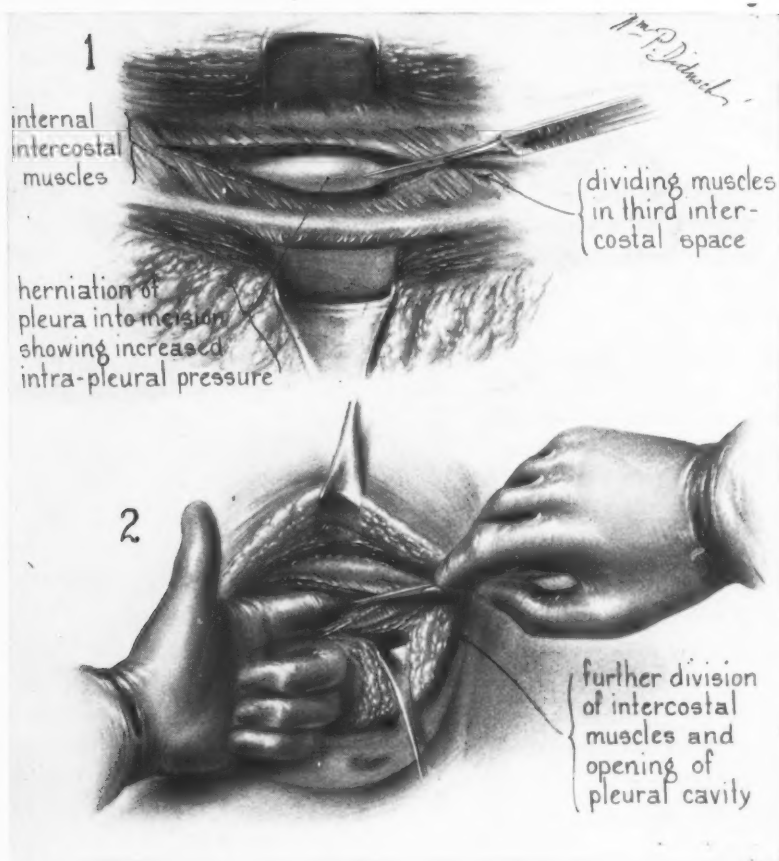


FIG. 2.—Showing entrance to thoracic cavity with minimum amount of damage.

Furthermore, physical signs were atypical and in unusual locations as regards the lung itself. Lobar, broncho or interstitial pneumonia, as a rule, present fairly typical physical signs. This is not the case in pneumonitis due to bronchial obstruction associated with primary carcinoma of the lung. The explanation for these unusual observations is not far to seek when their pathogenesis is considered. When obstruction of a bronchus, whether primary, secondary, tertiary or quaternary occurs as a result of a new growth, alone or in

CARCINOMA OF LUNG

association with a mucus plug, the bronchial tree peripheral to the point of occlusion becomes filled with mucus. Eventually infection of this bronchopulmonary segment occurs and the clinical syndrome of localized pneumonitis is produced. A portion of a lobe of greater or lesser dimensions, the entire lobe or even the entire lung may be involved. If exacerbations of such a pneumonitis are of sufficient frequency, bronchiectasis, or even an abscess, will at times supervene. Often such an abscess perforates into the pleura and produces putrefaction empyema. The point to be emphasized is that when such an unusual sequence of events takes place, or when any one of the previously-mentioned inflammatory episodes occurs that cannot be explained as a complication of a typical pneumonia or as a result of aspiration of a foreign body, an intrabronchial growth should be suspected. It is the repetitious nature of such pneumonitis which makes it so significant.

In general, it may be stated that there are no characteristic or pathognomonic signs and symptoms of primary carcinoma of the lung. This lesion masquerades as many of the more common disorders of the lung. The onset is often insidious, but the recurrent nature of signs and symptoms previously described should call attention of the patient and the physician to the respiratory tract so that a thorough examination will be carried out. Especially is this true of a patient who has previously had excellent health and in whom, after the second decade, there develops a cough associated with spitting of blood. Too often precious time is lost because of a diagnosis of pulmonary tuberculosis, lung abscess, unresolved pneumonia, bronchiectasis or heart disease. The methods of examination employed to rule out the presence of an intrabronchial growth in no way interferes with the diagnosis or treatment of any of the conditions which are at times mistaken for such a growth.

Diagnosis.—In this series of 327 cases the roentgenograms of the chest were positive in every instance. It is not suggested that a diagnosis of primary carcinoma of the lung could be made from the roentgenographic studies alone, but there was in each case an abnormal shadow which necessitated further study and examination. Thus, it may be stated emphatically that in every instance in which roentgenograms of the chest show a departure from normal, and in which this departure is not in every way characteristic of one of the commoner lesions of the lung, the presence of bronchogenic cancer should be inferred. Unquestionably, the roentgenograms of the chest are the most important and simplest method of examination at our disposal. Even in the earliest stages of growth of a primary carcinoma of the lung the lesion, as a rule, can be discovered. In the early part of the last decade, and even today, it was, and is, disheartening to watch an early lesion develop over a period of months into an inoperable cancer of the lung because physicians who were not, and are not, aware of this danger would advise the patients to "wait and see what happens." "Coming events often cast their shadows before them"—it is equally true that shadows cast by hilar infiltration due to other conditions, such as tuberculosis and even normal structures, are confusing. However, an infiltrating hilar shadow in a patient past middle age, associated with cough,

hemoptysis and the absence of tubercle bacilli in the sputum almost certainly indicates a bronchogenic carcinoma; most of these carcinomas are located at or near the hilus or root of the lung. The diagnosis of cancer of any organ cannot be definitely made by roentgenologic examination alone, but the more experienced the observer the greater the likelihood of an accurate interpretation. Positive roentgenograms may show a shadow produced by the new growth itself or by an area of atelectasis, bronchiectasis, pneumonitis or abscess caused indirectly by occlusion, by the growth, of a bronchus leading to a bronchopulmonary segment or segments.

In my experience, second to the roentgenogram in importance in yielding information which is helpful in arriving at a definite diagnosis is bronchoscopy. In fact, either by direct vision or biopsy or both a positive diagnosis of primary carcinoma of the lung can be made only in this manner. In 70 per cent of the patients in this series a positive biopsy of the cancer was obtained. A pulmonary new growth in the periphery or even in the hilar lesions confined to the upper lobes may be beyond the vision of the bronchoscopist. Nevertheless, valuable information can be elicited by bronchoscopy even when the growth cannot be seen, such as fixation or deformity, or both, due to pressure of any visible portion of the bronchial tree. The presence of blood or purulent discharge from certain bronchi serve as a lead. In this series of cases there have been no untoward results during or after bronchoscopic examinations.

Bronchography is a useful diagnostic method only to reveal occlusion of a bronchus by a small growth which does not produce a shadow in the roentgenograms of the chest. However, it is a harmless procedure and may be the link in the chain of evidence pointing to the possible presence of carcinoma of the lung.

Aspiration biopsy has a limited field, is often difficult to interpret, and such procedures are not without danger of implanting some cells along the tract of the aspiration needle or infecting the pleural cavity with the same cells, with tubercle bacilli or other pyogenic organisms. Aspiration of the bronchial tree has in some instances revealed cancer cells which could be obtained for microscopic examination.

Exploratory thoracotomy should be resorted to far more frequently in the future than it has in the past. This is, with the present-day anesthetics and surgical technic, a relatively harmless procedure—far more so than exploratory celiotomy and attended with fewer dangerous sequelae, such as adhesions. Exploratory thoracotomy is far less incapacitating than celiotomy. When it has been impossible to arrive at a definite diagnosis by all the means at our disposal this procedure should be performed at once, if a dangerous pulmonary lesion such as primary carcinoma is suspected. In our series of cases no deaths have occurred as a result of simple exploration of the chest. If direct observation and palpation of the lesion does not reveal the true nature, excision of the entire area in the lobe should be performed for immediate microscopic examination, and the diagnosis is made as is customary for questionable cases of carcinoma of the breast. If further discussion of the sit-

CARCINOMA OF LUNG

uation with the patient seems advisable, the wound may be closed and the patient returned to his room for further consultation. Later in the week the chest can be reopened and the definite procedure carried out. The old idea that opening the thoracic cage at operation is another form of euthanasia must be abandoned. The impression that all primary malignant tumors of the lung are slow-growing and late in metastasizing is incorrect.

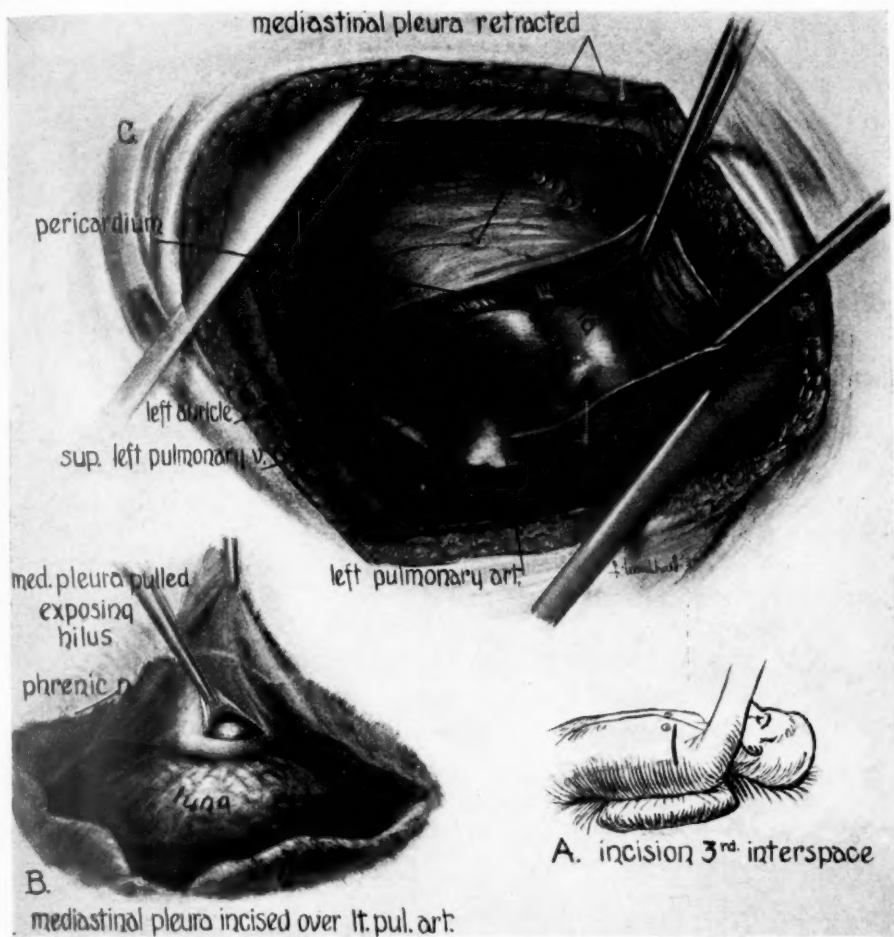


FIG. 3.—Exposure of hilar structures on the left side through anterior approach. Note ease of exposure of pulmonary artery, aorta and pulmonary veins.

Pathology.—The surgical removal of primary carcinoma of the lung in a relatively early stage has brought about changes in our ideas of the origin and nature of the growth of such tumors. In the past practically all the data were based on the autopsy in very late cases, when it was impossible on account of the almost universal involvement of the lung and contiguous structures to determine the nature, origin and progress of the growth within the lung. In this

series of cases the tumors occurred at or adjacent to the hilus, the minority in the periphery of the lung. The latter seemed to spread throughout the area of the lung in which they originated by centrifugal growth, most of them apparently having arisen in the alveolar lining cells. The hilar tumors, all of which were bronchogenic in origin, grew grossly in two separate fashions. The one, an intrabronchial tumor arising apparently from the bronchial mucosa, grew into the lumen of the bronchus and towards the trachea. The centripetal tendency of the growth, occluding completely or partly the primary or secondary

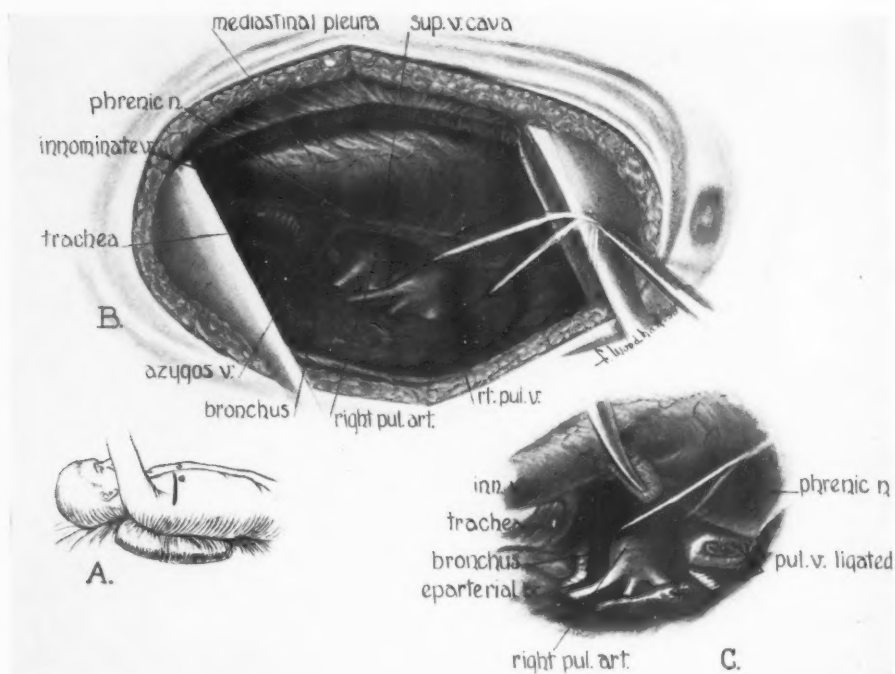


FIG. 4.—Exposure of hilar structures on right side. Pulmonary vessels lying anterior to bronchus are readily demonstrated.

bronchus was characteristic. The other type of hilar growth was an extra-bronchial tumor which, probably arising in the wall of a secondary, tertiary or quaternary bronchus, would break through the wall and grow along outside of, and often completely around, the bronchus. This type of growth, also, showed this centripetal tendency, growing around and about the secondary and primary bronchi and then spreading directly into the mediastinum to involve the structures contained therein.

The clinical course is dependent to a great extent on the method of growth. It is, of course, obvious that the intrabronchial type will produce respiratory difficulties, cough, sputum, and hemoptysis much earlier than the extra-bronchial tumor. The first symptoms caused by the latter method of growth may be, for example, interference with the venous return from the neck owing

to the involvement of the superior vena cava on the right side, or recurrent laryngeal palsy on the left, or Horner's syndrome. Malignant tumors arising in the periphery are, as a rule, asymptomatic. They may be said to arise in the silent area of the lung and as they do not, as a rule, produce bronchial obstruction or erode pulmonary vessels the symptoms and signs are usually those dependent on invasion of the pleura and chest wall and, by direct extension, the brachial plexus.

In 70 per cent of the 112 patients upon whom a total pneumonectomy was performed there were metastases to the bronchial and tracheal lymph nodes. This fact emphasized the necessity of performing a total pneumonectomy with dissection of these regional nodes in order to effect a permanent cure. In the remaining 215 cases that were inoperable, in addition to the metastases in the regional nodes the various organs and structures that were the site of metastases are listed in the order of the frequency of their involvement: supraclavicular and axillary lymph nodes, liver, pleura, pericardium and heart, contralateral lung, osseous tissue, brain and multiple areas in the skin and subcutaneous tissue.

The characteristic histologic structure of the tumor occurring in this series of cases was that of a flat and squamous cell carcinoma and adenocarcinoma. Under these two main headings were included various examples such as oat cell, cylindrical cell and adenocarcinoma thought to be different forms of the same tumor. The adenocarcinoma type is pleomorphic. Sections of the tumor differ depending upon the region from which they were cut. Sixty-five per cent of the cases in this series were composed of a flat or squamous cell cancer and 35 per cent the adenocarcinoma group.

It is interesting to note that the length of life, computed on the basis of the microscopic characteristics of the tumor, showed that those afflicted with the squamous, or flat cell type, lived a greater length of time than those with the adenocarcinoma type.

Treatment.—Preoperative Preparation: For several days preceding operation the patient should be carefully prepared. It has been our custom to treat the patient with intramuscular injection of penicillin 30,000 units, every three hours, avoiding awakening the patient at night. In addition to this penicillin aerosol should be employed. Whether or not some of the sulfonamides should be used has been questioned. It is my personal opinion that for some days, approximately three, sulfamerazine may be administered by mouth. The patients, thus, have a protective blood level of this drug which apparently does no harm. It is merely an added questionable merit and so far we have not been able to observe any demerits.

However, the preoperative preparation which we consider of the greatest importance is the induction of artificial pneumothorax. The advantage of this procedure has been proved over a period of years. In the first place, it must be considered a therapeutic test, particularly in individuals in the fifth or sixth decade in which there may be a certain degree of unrecognized emphysema. Removing the lung at operation without knowing whether or not the patient

can sufficiently oxygenate himself with the remaining lung may constitute a fatal error, and in the past we have experienced this tragic result. The ability of the remaining lung to function sufficiently for the needs of the patient can be established before operation is performed by merely collapsing the lung on the affected side. Various tests, such as oxygen saturation of the blood at body rest and during exercise of various degrees of intensity can be ascertained. For

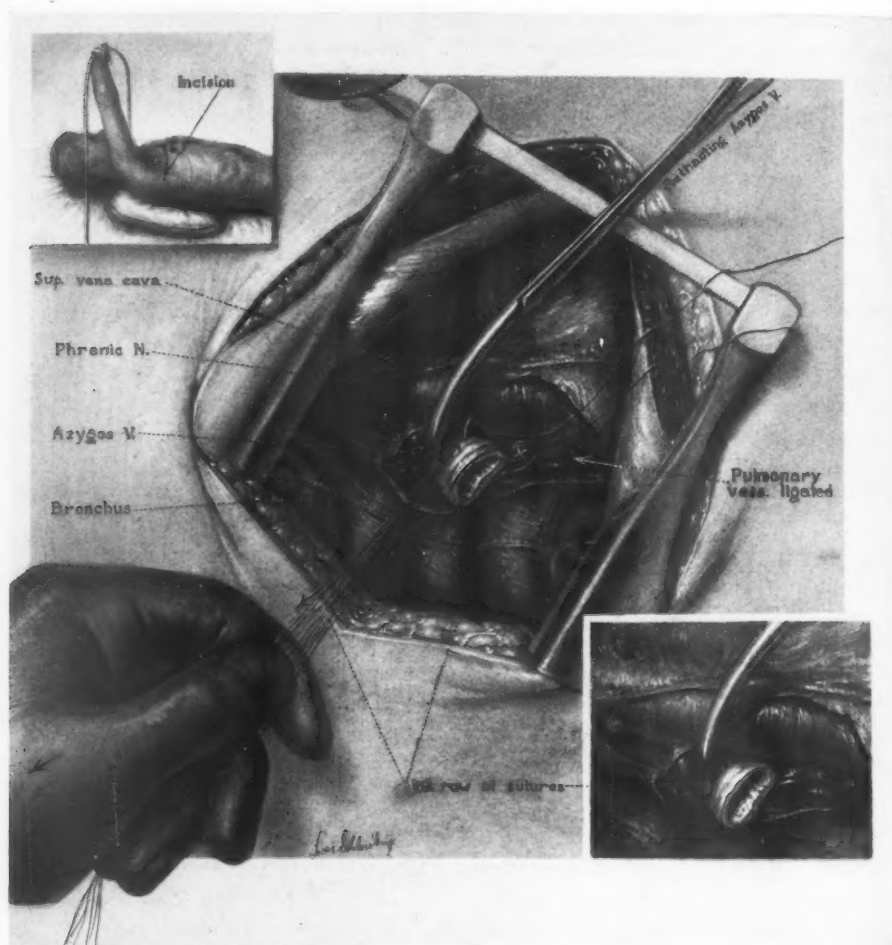


FIG. 5.—Demonstrating placing of interrupted mattress sutures occluding bronchus 1 cm. proximal to cut end. Note cuff-like portion of bronchus distal to suture line.

after all to cure a patient of a malignant tumor of the lung is futile, if the patient is left with insufficient aeration surface to support normal respiration. There are other minor advantages and secondary ones associated with artificial pneumothorax, such as diminishing the size of the lung so that the mechanical handling of this structure is technically made easier at the time of operation. Second, the patient has learned to breathe with one lung previous to operation

CARCINOMA OF LUNG

and with the increased intrapleural pressure, thus, avoids pleural shock on opening the thoracic cavity. Third, the blood flow through the collapsed lung is less than through the expanded contralateral lung and, therefore, the strain on the right heart from shifting greater blood flow through one pulmonary artery is graduated. Fourth, the location of a growth as regards the position relative to the mediastinum is often silhouetted and, therefore, located more accurately in the collapsed lung than with an expanded lung.

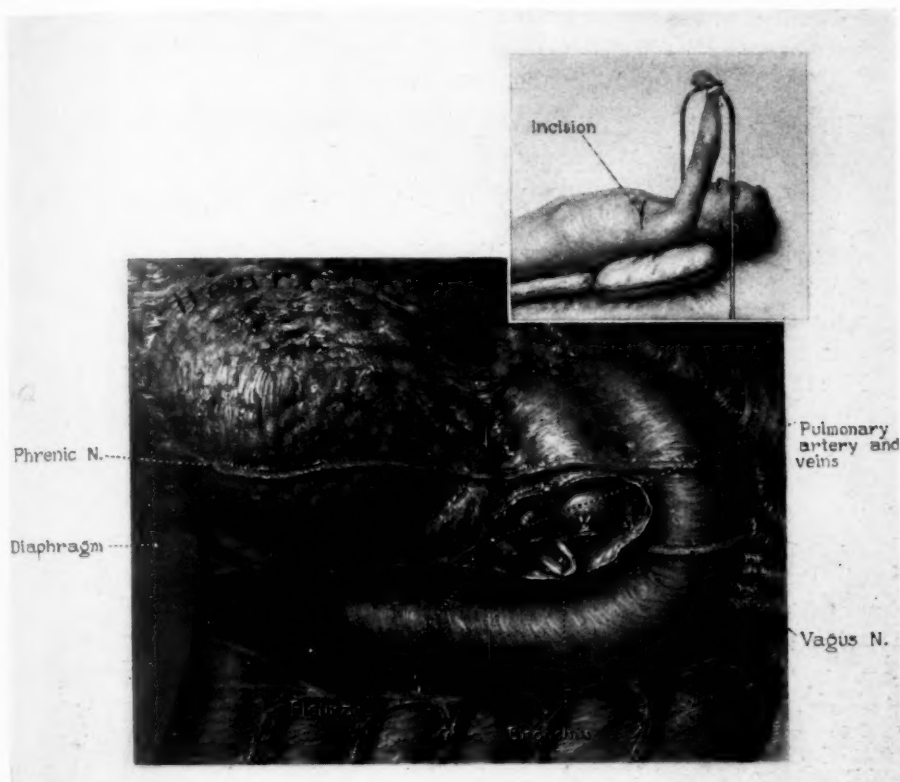


FIG. 6.—Lung amputated, hilar structures ready to be pleuralized, showing relation of pulmonary vessel to bronchus. Open cuff of bronchus visible.

Treatment.—In our present state of knowledge the only efficacious method for treatment of pulmonary carcinoma is by surgical removal of the entire organ, together with the regional lymph nodes. Medicinal and radiation therapy are only palliative, and as these tumors are, as a rule, radio-resistant, radiation therapy is of no benefit. It is interesting to note that in 215 cases of this series which were found to be inoperable at the time of exploration of the thoracic cavity, the average length of life after leaving the hospital was approximately five months, and this in spite of the fact that every type of supportive therapy, and in many instances, radiation therapy, were employed. It is to be emphasized again that the disease runs a fatal course in 100 per cent of the

patients in whom the lung cannot be removed in its entirety by operation. From an anatomic standpoint, the lung lends itself to surgical removal more readily than any other organ in the body, with the possible exception of the breast. From the point of view of the biologic characteristics of primary carcinoma of the lung surgical removal is more apt to be successful because of the relatively slow growth and spread of these tumors as compared to similar tumors in other regions of the body. Finally, the remarkable ability and tendency of the contralateral lung to undergo compensatory changes prevents incapacitation of the patient from a physiologic point of view.

OPERATIVE TECHNIC

The operative technic now employed for one-stage total pneumonectomy in the treatment of malignant tumors is essentially the same, except for closure of the bronchus, as that described by the author in 1933 in the Johns Hopkins Hospital Bulletin.¹

A number of points in the operative technic, as would be expected, are still controversial and as in any other operative procedure a unanimity of opinion as regards the various methods is hardly to be expected. But, after 13 years' experience and having employed this operative technic in 327 cases, of which 112 were total pneumonectomies, it is felt desirable, with the background of this experience to discuss certain steps in the operative procedure which are of special interest.

In the first place, the anterior approach is definitely to be preferred to the posterior or lateral for the following reasons: (a) the width of the intercostal spaces is greater anteriorly than posteriorly and the necessity for resection of ribs is, therefore, as a general rule, not necessary. This reduces the operative time and the general ill effects of the procedure upon the patients (Figs. 1 and 2). The thoracic cavity is more quickly entered with a minimum amount of damage to the chest wall and parietes. The use of a self-retaining retractor gives sufficient exposure so that the question of operability can be promptly judged. The time consumed from the incision to the entrance of the pleural cavity is far less when the anterior approach is employed, and associated with this there is a minimum loss of blood as well as trauma to tissues. If a greater amount of exposure is desired the adjacent intercostal cartilages can be incised and the ribs, usually the third and fourth, can be displaced cephalward or caudalward. Also, by slightly rotating the patient on the operating table, or the table itself, if desired, the incision can be extended laterally so that the maximum exposure can be obtained. If the tumor proves to be inoperable, the minimum of operative trauma has been incurred. The operability can be determined at once with the minimum operative effort. In the event the growth is operable the dissection of the hilar structures, such as the pulmonary artery and veins which lie anterior to the bronchus, is accomplished with far greater ease and facility when the anterior approach is employed (Figs. 3 and 4). The advantage of ligating the pulmonary artery at the beginning of the operation is obvious, the control of hemorrhage is, thus, more certainly

CARCINOMA OF LUNG

assured and the greater percentage of blood normally contained within the lung is returned to the general circulation *via* the pulmonary veins. Bleeding from any adhesions that may exist between the visceral and parietal pleura is reduced to a minimum. If for any reason it is felt desirable to interrupt the operative procedure and perform the operation in two stages, one can do so after ligation of the pulmonary artery, provided the pulmonary veins have been left intact. If the latter are ligated, the lobe which either one or both pulmonary veins drain, must be removed, for otherwise, gangrene of this portion of the lung will ensue. It is to be noted that the bronchial veins are vestigial in character and do not function sufficiently to even drain off the blood brought

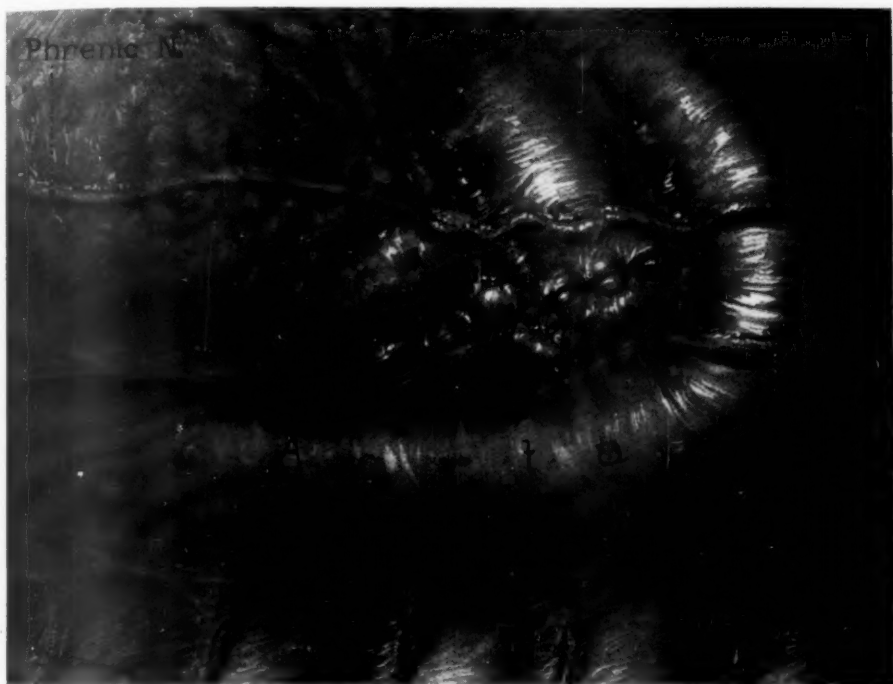


FIG. 7.—Left side of bronchus, plus denuded hilar surface covered with pleura.

to the lung by the bronchial artery, to say nothing of that from the much larger pulmonary artery. When the pulmonary artery, which carries venous blood is ligated collateral circulation through the bronchial artery is at once established. The bronchial artery brings sufficient arterial blood to the lung to maintain this organ in a normal state of nutrition and the circulation through the lung is, thus, changed from a venous to an arterial one. Whereas normally the greater amount of blood flowing through the lung capillaries is venous in character, originating from the pulmonary artery, the blood flowing into the same capillary bed from the bronchial artery is arterial. Stoppage of the blood flow from the pulmonary artery by ligature of the latter, incurs a great increase in

flow from the bronchial artery and, thus, fills the capillary bed in the lung and the branches of the pulmonary artery up to the point of ligation with arterial blood, containing such a high saturation of oxygen that the lung is, thus, rendered essentially functionless as far as further oxygenation of the blood flowing through it is concerned. The development of this collateral circulation *via* the bronchial artery begins after ligation of the pulmonary artery is performed. In the early days simultaneous ligation of one or both pulmonary veins invariably resulted in moist gangrene of the corresponding lobe or lobes because of the vestigial character of the bronchial veins. In the event of ligation of a pulmonary vein that portion of the lung whose venous bed is a tributary to that vein must be removed at the time of operation.

Not infrequently total pneumonectomy may be carried out with a greater degree of safety if a two-stage operation is performed, in which only the pulmonary artery is ligated as the principal objective of the first stage. This is particularly true when the lung is the site of a great deal of infection and extensively adherent. The arterialization of the lung with a flow of more highly oxygenated blood would appear to have a beneficial effect on the pulmonary infection and, therefore, the patient's clinical condition.* Dividing the operation into two stages greatly diminishes the shock of the procedure. It has been found that the pulmonary vessels, the artery and veins, are best ligated with silk, or cotton, and in no instance has this type of ligature been known to cut through the vessel wall.

TREATMENT OF THE BRONCHIAL STUMP

Since 1942, when the method of closing of the bronchus was first reported by the author in the ANNALS OF SURGERY² the bronchial stump has been occluded by the use of mattress sutures of interrupted silk or cotton placed through the bronchus in such a manner that the posterior membranous portion is approximated to the anterior cartilaginous wall, somewhat proximal to the end of the amputated stump, thus, creating a viable cuff from 1 to 2 cm. distal to the suture line which immediately fills with a fibrinous clot that thereafter becomes infiltrated with cells and eventually forms a fibrous plug (Fig. 5).

* In patients suffering from pulmonary tuberculosis ligation of the pulmonary artery has a definite deleterious effect. In eight patients the pulmonary artery was occluded with the idea of bringing about an atelectasis of the lung. The lesions were very extensive in each case and associated with large cavities. However, the change from a lower oxygen tension in the blood flow through the lung following ligation of the pulmonary artery, to the higher oxygen content of the blood flow from the bronchial artery exercised a most marked detrimental clinical and pathological effect on the patient and lung. This was apparent by a more rapid progression of the manifestation of the disease than would have been expected had the pulmonary circulation not been interfered with at all. No atelectasis was produced and cavitation increased rapidly. This unfavorable result was attributed to the fact that the tubercle bacillus flourished in an environment of higher oxygen content. It would be interesting to find out the effect of ligation of only the bronchial artery in pulmonary tuberculosis. The reverse condition of oxygen saturation would then obtain.

CARCINOMA OF LUNG

One of the more important steps in securing a satisfactory closure of the bronchial stump is to sew a pedicle flap of parietal pleura over the end of the stump of the bronchus approximating the pleura to the rim of the viable cuff. The use of any form of cauterization or traumatization to the end of the bronchial stump has been studiously avoided in order that agglutination of the rim of this cuff and the pleural membrane would be brought about immediately and permanently. Any foreign material such as sutures in the end of this cuff or devitalization of the rim of this cuff will militate against the immediate healing. Therefore, the bronchial stump should be sutured at least a centimeter

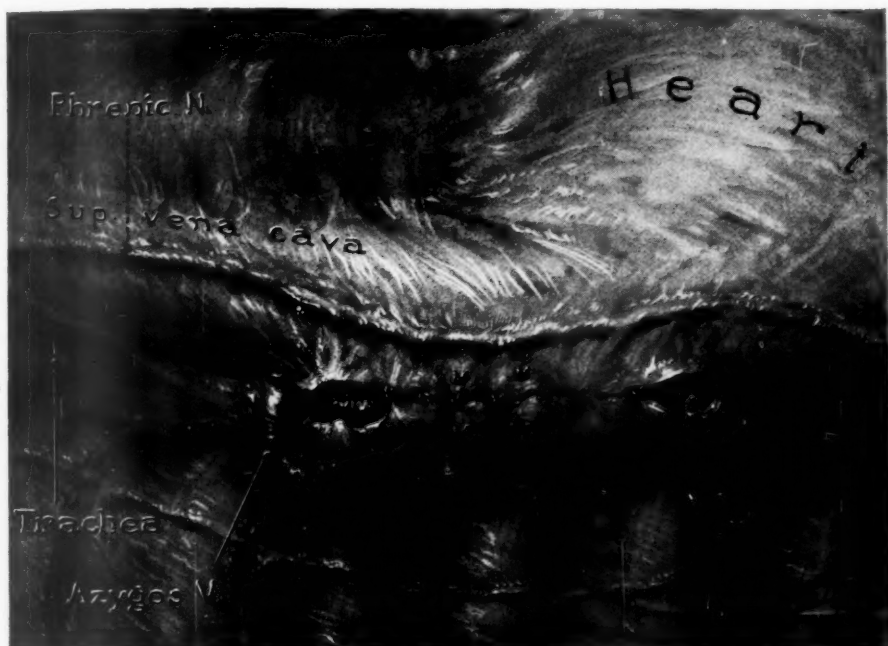


FIG. 8.—Right side of bronchus, plus denuded hilar surface covered with pleura.

proximal, if possible, to the point at which amputation is anticipated. Regardless of the type of suture material or the manner in which it is placed, cutting through the posterior or anterior membranous portion of the bronchus will frequently occur. This has been proved experimentally and at autopsy² (Fig. 6). Unless every opportunity is, therefore, afforded for the bronchial cuff distal to the suture line to heal by the formation of granulation tissue within its walls leakage will follow in a rather high percentage of cases. In the event that the bronchial growth extends up toward the carina, the bronchus and also the lower end of the trachea may be sutured after a diagonal incision in this structure has been made. This suture, as in the bronchus, should be tied sufficiently tight to approximate the walls of the bronchus or trachea, but not enough to cause crushing of the tissue. If so, the sutures will cut. They should also be

placed so that the knots are tied about the cartilaginous rings, that is on the anterior surface of the bronchus or trachea. Healing of the stump takes place at the cut end and the sutures which occlude the lumen of the bronchus, usually from four to six in number, must be considered as only temporary, with their main purpose to exclude the passage of air through the bronchial stump long

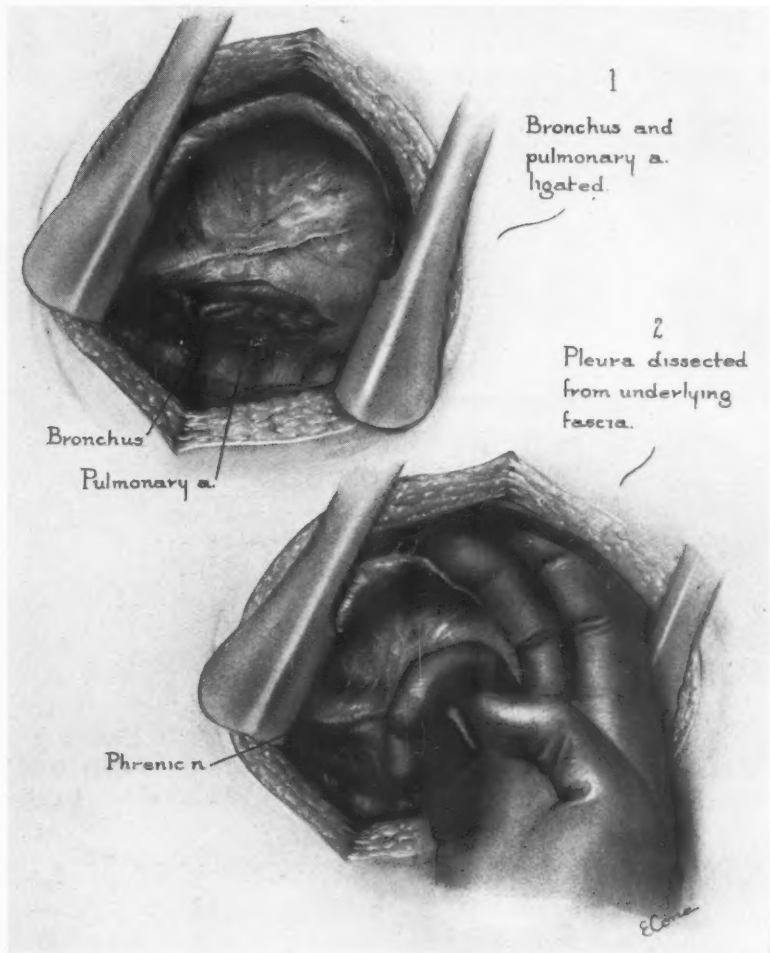


FIG. 9.—Mobilization of pleura over anterior chest wall, developing flap of parietal pleura to cover raw area of hilus. The same method can be used in mobilization of the parietal peritoneum over the vertebral gutter.

enough for the healing of the end of the bronchus to be completed, or sufficiently so, that in the event the sutures cut through, to form a tight and impenetrable occlusion of the bronchial stump that will not open up and allow air to pour into the pleural cavity. The healing of the end of the bronchial stump requires, as a rule, from one to two weeks, varying in different individuals, and seems to be completed in the majority of cases after a period of 10

CARCINOMA OF LUNG

to 14 days. However, there have been instances in our series in which the stump in one patient reopened after a month, one after three months and one even after eight months. However, these, fortunately, eventually healed and the patient was none the worse off except for the disagreeable experience asso-

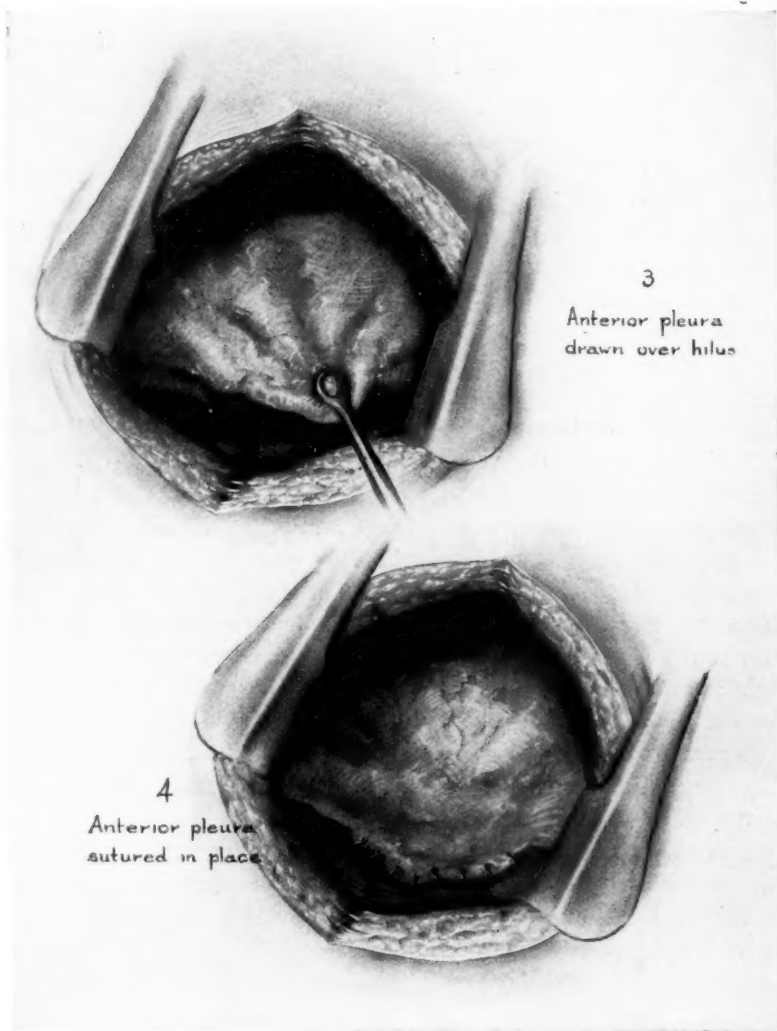


FIG. 10.—Mobilization of pleura over anterior chest wall, developing flap of parietal pleura to cover raw area of hilus. The same method can be used in mobilization of the parietal peritoneum over the vertebral gutter.

ciated with walled-off empyema, which was satisfactorily treated by drainage and irrigation with penicillin.

Interrupted mattress sutures may be employed by stitching the anterior cartilaginous wall laterally, infolding the posterior membranous portion, pro-

viding the cartilaginous rings are incised at the apex of their arc, this in the midline of the anterior surface of the bronchus. This method has been satisfactorily employed in some cases. (Fig. 7-Fig. 8.)

All types of suture material have been used—catgut, silver wire, steel wire, fascia, and others—and it is our opinion that interrupted sutures of silk or cotton would seem to be the material of choice.

Before the bronchial stump is sutured, after amputation of the lung, the inside of the remaining bronchus should be carefully inspected, for not infrequently a blood clot or even a piece of tumor tissue may be dislodged from the lung into the primary bronchus during the course of the operation. Immediately following operation the patient is again bronchoscoped while on the operating table before being returned to the ward. Often small clots and pieces of tumor tissue have been discovered not only in the bronchial stump on the operative side but even in the trachea. If these foreign bodies were not removed, aspiration into the contralateral lung might eventuate in the death of the patient.

Mobilization of the parietal pleura may be accomplished on either side by loosening the pleura from the endothoracic fascia either anteriorly or posteriorly in the vertebral gutter. No difficulty has been experienced in obtaining a sufficient amount of pleura to cover over completely and without tension the entire raw hilar area (Figs. 9 and 10).

At the end of the operation 150,000 units of penicillin have been introduced into the thoracic cavity. The intrapulmonary pressure, as the wound in the chest wall is closed, has been increased to not more than 10 mm. of mercury. The entrapped air is removed to the fullest extent possible by leaving a small catheter in the wound during closure. After the last interrupted suture is placed in the skin all the air that can be is removed by aspiration and the catheter itself is then withdrawn. No drainage of the pleural cavity is thought desirable even in the presence of infection, within the lung itself, and when purulent material has been unfortunately and accidentally spilled into the pleural cavity.

Since penicillin has been available, when gross infection has been present it has been our custom to introduce every other day 50,000 units of penicillin into the thoracic cavity. In addition, the drug is also given intramuscularly up to 50,000 units every three hours. No instances of empyema have been encountered in cases so treated, and, thus, the necessity for performing thoracoplasties to obliterate infected dead space in the thoracic cavity has been avoided.

A word of caution should be given here in regard to the possibility of the development of interstitial pulmonary emphysema as a result of increasing the intrapulmonary pressure either too rapidly or to too great an extent, in an endeavor to hyperdistend the lung on the unoperated side for the purpose of obliterating the dead space in the thoracic cavity on the operative side. Rupture of alveoli within the lung substance itself producing a mediastinal, plus extensive subcutaneous as well as visceral emphysema was encountered in one

CARCINOMA OF LUNG

case of diaphragmatic hernia followed by death from cerebral and coronary air emboli, proved at autopsy.

The final proof of the efficacy of any method of therapy naturally is a critical analysis of the immediate and remote results. Of 327 cases of primary carcinoma of the lung, as shown in Table III, 215, or 66 per cent, were inoperable, whereas, 112, or 34 per cent, were operable. This ratio of the inoperable to the operable cases is far higher than it should be, for in the majority of instances the attending physician and even the patients had been aware of a lesion in the lung for many months, and often years, before submitting themselves to operation. Undoubtedly in the future, as the field of thoracic

TABLE III
CARCINOMA OF THE LUNG
Ratio of Operable to Inoperable Cases

	No. of Cases	Percentage
Operable.....	112	34
Inoperable.....	215	66
	327	100

TABLE IV
CASES OF INOPERABLE CARCINOMA
According to Years

	No. of Cases
1934.....	2
1935.....	3
1936.....	9
1937.....	17
1938.....	22
1939.....	14
1940.....	21
1941.....	16
1942.....	22
1943.....	19
1944.....	19
1945.....	37
1946.....	14
Total.....	215

surgery is developed, this disproportion will be reduced. There will always be those instances in which a malignant tumor begins in the periphery of the lung, the so-called silent area, and produces no symptoms or signs until involvement of the pleural or contiguous structures renders the case inoperable. Fortunately, this group comprises only about 10 per cent of the cases of malignancy of the lung, 90 per cent occurring near the hilus, and producing warning signals early in the process of the disease. Unless for palliative reason, to rid the patient of an infected lung due to neoplastic bronchial obstruction, for example, pneumonectomy should not be performed if the tumor has involved contiguous structures. Therefore, inoperability would be manifest by involvement of the parietal pleura or any of the underlying structures.

Table IV reveals the number of cases, *i.e.*, 215, of inoperable carcinoma of the lung which have been subjected to operation from January, 1934 until July, 1946. This number does not include those patients that were clinically inoperable. The clinical findings, which we have found to indicate a spread of the tumor beyond the confines of the lung and, therefore, render the case incurable from a surgical standpoint, are the following: Metastases to the opposite lung or mediastinum, direct metastases to brain, osseous tissue, liver, skin, axillary and supraclavicular nodes, pleural effusion, clear or serosanguineous, continuous pain to shoulder or referred down the arm, Horner's syndrome, left recurrent laryngeal palsy or hemiparalysis of the diaphragm.

TABLE V
PNEUMONECTOMY FOR CARCINOMA OF THE LUNG
Operations and Mortality According to Years

	No. of Operations	No. of Deaths
1933.....	2	0
1934.....	1	1
1935.....	5	1
1936.....	4	2
1937.....	5	0
1938.....	7	2
1939.....	6	2
1940.....	10	0
1941.....	13	3
1942.....	9	4
1943.....	9	2
1944.....	12	2
1945.....	15	5
1946.....	14	1
	<hr/> 112	<hr/> 25

Although the number of cases of inoperable carcinoma of the lung have apparently increased since 1939, when Table IV is compared to Table V, there is very little fluctuation in the ratio of operable to inoperable cases over the same period of time. All patients with lesions of the lung which have been diagnosed probable malignant tumors should be explored regardless of the size or position of the tumor or the age of the patient. In the absence of clinical signs or symptoms of a spread of the disease from within the limits of the lung itself, the question of operability can be determined only by exploration of the chest.

In this series of cases, there have been 107 in which total pneumonectomy was performed for carcinoma of the lung.

Table V represents the number of total pneumonectomies performed each year for carcinoma of the lung, together with the deaths occurring within one month of the operation. All deaths within this time limit were considered in the group of immediate postoperative mortality because of the fact that the patients had remained in the hospital that long and although in some instances death was in no way connected with the actual operative procedure. From

CARCINOMA OF LUNG

1933 through 1939 there were 30 cases with eight deaths, or a mortality of 27 per cent. From 1940 through half of 1946, 82 patients were operated upon, with 17 deaths, or a 20.7 per cent mortality. Thus, in spite of an increase in the number of patients there was a 5 per cent decrease in immediate postoperative mortality. Undoubtedly in the future this hospital death rate will be decreased because of several reasons, such as earlier reference of cases by the general practitioners, improvements in operative technic, chemotherapy and anesthesia. In addition, postoperative care has improved remarkably. Penicillin is now given intramuscularly, by inhalations, and intrathoracically, so that the chance of developing a postoperative empyema is almost *nil*.

TABLE VI
PNEUMONECTOMY FOR CARCINOMA OF THE LUNG

	No. of Cases	Total	Percentage
Patients dying after various periods of time:			
Less than 1 month.....	25	25	22
1 month to 6 years			
1 month to 6 months.....	20		
6 months to 1 year.....	10		
1 year, or more.....	6		
2 years, or more.....	2		
3 years, or more.....	3		
4 years, or more.....	1		
5 years, or more.....	1		
6 years, or more.....	1	44	39
Patients living:			
1 month to 6 months.....	12		
6 months to 1 year.....	2		
1 year, or more.....	8		
2 years, or more.....	5		
3 years, or more.....	4		
5 years, or more.....	4		
6 years, or more.....	2		
9 years, or more.....	2		
10 years, or more.....	2		
11 years, or more.....	1		
13 years, or more.....	1	43	39
		112	100

Important as the immediate operative mortality is, and it should be very jealously guarded, the efficacy of the operative procedure should also be judged by the ultimate results. The duration of life following total pneumonectomy for carcinoma of the lung is shown in Table VI. It is to be noted that patients dying after various periods of time are so charted in comparison to patients still living following operation. Those dying following operation who died less than one month afterwards were considered an operative mortality. The total operative mortality of the 112 cases for total pneumonectomy for carcinoma of the lung was 22 per cent. Of the patients who are now dead, but who lived for various periods of time after operation, *i.e.*, from one month to six years, the number surviving the different periods of time was 44. This group of cases made up 39 per cent of the total. Reference must be made to the fact that of the 215 cases of inoperable carcinoma comprising this series,

the average duration of life after exploration of the thoracic cavity was five months, so that even in the group, in Table VI, which are now dead but lived various periods of time following operation, the average duration of life after removing the lung was greater by far than in those patients in which the lung could not be removed. Of the patients living at the present time, 39 per cent of the total, or 43 patients, have survived from one month to 13 years. Of this group, 12 patients have lived five years, or more; one, 13 years; one, 11; two, nine; and two, six. As they are still living there is a possibility they may live for many years. It would seem desirable to call attention to the fact that all these patients, except one who was a professional boxer, have been restored to their normal activities. They have been able to return to their former vocations and even recreations, such as golf, swimming, fishing and hunting. In all except the occasional case, since it has not been found necessary to perform a thoracoplasty, no deformity of the patient is visible from the removal of the affected organ. The remaining lung expands to fill the dead space. This intrathoracic readjustment has been reported in detail elsewhere. If these results are compared to those obtained from the surgical treatment of carcinoma of the thyroid, breast, esophagus, stomach and large and small intestine, reported over a corresponding length of time (13 years) it will be evident that removal of the lung for primary carcinoma offers at least as great if not greater probability of permanent cure as the surgical treatment of carcinoma of any other organ in the body.

Of the group of patients who lived for some time (up to six years) following operation, but who are now dead, the majority were definitely improved by relieving the coughing, hemoptysis and often extensive pulmonary suppuration with its attendant discomfort and manifestations.

CONCLUSIONS

An otherwise fatal disease, primary carcinoma of the lung, can be satisfactorily treated by surgical removal of the entire organ. Surgical measures short of total pneumonectomy are not efficacious. Postoperative mortality and longevity are at least as good as, if not better than, the postoperative results following the surgical treatment of carcinoma of other organs.

REFERENCES

- ¹ Rienhoff, William F., Jr.: Pneumonectomy: A Preliminary Report of the Operative Technic in Two Successful Cases. *Bulletin of the Johns Hopkins Hospital*, 53, No. 6, 390, 1933.
- ² Rienhoff, William F., Jr., Gannon, James, Jr., and Sherman, Irwin: Closure of the Bronchus Following Total Pneumonectomy: Experimental and Clinical Observations. *ANNALS OF SURGERY*, 116, No. 4, 1942.

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DISCUSSION.—DR. BRIAN BLADES, Washington, D. C.: I fully agree with Doctor Ochsner and Doctor Rienhoff that the indications for exploratory thoracotomy in patients suspected of having a neoplasm of the lung, should be extended. I understood Doctor Ochsner to say that the only contraindication to exploratory operations at his Clinic was evidence of distant metastasis. This brings up the question of whether or not one should

CARCINOMA OF LUNG

adhere to the contraindications observed a few years ago; namely, paralysis of the diaphragm, paralysis of the vocal cord, or the presence of a pleural effusion. Should exploratory operation be recommended to a patient with any of these manifestations of extension of the tumor and, particularly, should operation be recommended if a bloody effusion is present?

Certainly these two extensive series of pneumonectomy for bronchogenic carcinoma demonstrate the great progress which has been made in this type of surgery in the past ten years.

DR. ALTON OCHSNER, New Orleans, La. (closing): I should like to reiterate the point Doctor Rienhoff made. We feel that artificial pneumothorax is extremely important as a preliminary procedure. I think it allows the cardiovascular system to adjust itself to the collapse of the pulmonary capillary bed. I should like, also, to emphasize the importance of the anterior approach. With very few exceptions we use this approach; only in suppurative disease do we use the posterolateral approach. It is so much easier to operate through the anterior approach because the distance from the chest wall to the mediastinum is less than in the posterolateral approach. Doctor Rienhoff deserves the credit for popularizing this method of approach.

In answer to Doctor Blades' question, our only contraindication to operation is evidence of distant metastasis and evidence of pleural involvement. Pleural effusion is not a contraindication, but if the fluid is bloody, or if tumor cells are found in the centrifugated specimen, the case is considered inoperable. As to paralysis of the vagus or phrenic nerve, I do not believe it is necessarily a contraindication to exploration. One patient of ours who had survived operation for three years had recurrent laryngeal paralysis. She died subsequently, but to deny that patient the benefit of exploration would be to deny her several years of life. Some of these patients have involvement of the aorta. If this is true, the lung cannot be removed, but it is surprising how many times the involvement is such that one can resect the vagus and allow the patient to go a few months or years with comparative freedom from symptoms. Our contraindication to operation is evidence of extension beyond the lung into the parietal pleura or distant metastasis—not necessarily involvement of the phrenic or vagus nerve.

DR. WILLIAM F. RIENHOFF, JR., Baltimore, Md. (closing): Dr. Brian B. Blades asked whether one is ever justified in performing a lobectomy for carcinoma of the lung. Theoretically, and under quite unusual circumstances, I imagine this procedure would be warranted. I have known of only one case, operated upon by Dr. Edward Churchill, in which apparently a complete cure was obtained following lobectomy. Two brothers working under similar conditions developed malignant growths in the lung at about the same time. One succumbed because the growth was inoperable and the other was alive and well several years later following lobectomy. It is my opinion, however, that this case is the exception that proves the rule. I have been raised in the school of surgery in which eradication of the entire organ affected with carcinoma has been and is considered the proper surgical approach to this problem.

I agree with Dr. Alton Ochsner that the field of operability for carcinoma of the lung should be, and actually is being, extended. It just so happens that in those patients in whom a recurrent laryngeal palsy on the left side existed the tumor turned out to be inoperable. I think Dr. Evarts Graham successfully operated upon a patient in whom such a palsy existed prior to operation.

Dr. Alfred Blalock suggested that I mention briefly four patients that have been operated upon for solitary metastases. Two cases operated upon by me were instances of solitary metastases of a slow-growing fibrosarcoma originating in the tendon sheath of the thigh. Doctor Blalock successfully operated upon two patients in whom there were simple metastases from the colon. It is impossible to say how long these patients will live, but I am inclined to think that in the absence of metastases other than in one lung, one is perfectly justified in performing a total pneumonectomy.

A CONCEPT OF TOXIC GOITER*

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THYROTOXICOSIS is a constitutional malady of which we have incomplete knowledge obscured somewhat by therapeutic developments of the past quarter of a century. The ultimate outcome of its two forms, the adenomatous and the diffuse hyperplastic, may be essentially different, but it is well to consider them together, with frequent allusions to the features in which they differ.

Those of us who were operating upon toxic patients in the early 1900's realized that they gradually got ready for successful surgery, most of them, with treatment, without treatment, or in spite of treatment previous to Plummer's introduction of Lugol's solution in 1922, which very definitely shortened the preoperative period, which was still further shortened some 20 years later by the advent of the "thio-uro" group (potentially dangerous drugs).

Henry Plummer, of the Mayo Clinic, was the first to outline the *average* characteristic course of the disease as result of his analysis of 5,000 untreated patients. He demonstrated that the malady pursued a *cyclic* course, each cycle running about 15 months, of which the first half (7.5 months) showed decline in health, while the second half evinced spontaneous improvement. The patient sank to a lower level during each succeeding cycle, about ten of them being required to "*burn her out*." There are, of course, exceptions to all rules and I have seen two glaring ones of Doctor Plummer's. One young woman died in crisis within one week of her first thyrotoxic symptoms; another older woman experienced a free interval of 13 years between her first and second toxic episodes, then died in crisis during this last one.

An experienced goiter surgeon is frequently called in consultation over a patient dying in crisis, a situation which has, in my own experience, been precipitated invariably by one of two mental attitudes; namely, (a) impatience on the patient's part; or (b) ignorance on the surgeon's part that such a patient, treated or untreated, tends in most instances to become a safe operative risk if only he waits long enough.

The subject may well be considered under four heads:

1. Nature of the maladies.
2. Preoperative care of the patients.
3. Criteria of operability.
4. During and after operation.

The nature of the two maladies is similar in so many particulars that they may be considered together, insofar as six salient features are concerned; *viz.*,

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TOXIC GOITER

(1) Edemas are characteristic of both of them when they are at all advanced, due in great part, no doubt, to heart involvement at a period when no definite cardiac lesion can be made out. In diffuse hyperplasia the heart manifestations are likely to prove functional in character and to be promptly and completely relieved by thyroidectomy, while the toxic adenoma may produce *anatomic* lesions which tend to persist even after the goiter which produced them has been removed.

(2) Hypoproteinemia is practically characteristic of both forms of toxic goiter, hence, furnishes one of our leading motives in the preoperative care of every toxic patient. The objective here can usually be met by a sufficiently prolonged feeding of 115 Gm. (calculated) daily of the albuminous foods given to the ordinary hospital patient.

(3) Radiation of body heat is affected in all of these patients. One of the most common and most bitter of their complaints is occasioned by the circumstance that they can not get rid of it at a normal rate. We have been greatly aided in the preparation of such patients for operation by resting them on a veranda (weather permitting) placing them upon a canvas cot instead of a mattress, then using a fan most carefully.

(4) Anoxemia on Exertion.—This manifestation is usually of extreme degree in patients who present the other well-known features of the malady, especially in the diffuse hyperplastic form. The well-known Army "hopping up and down" exercises will readily elicit this symptom if present in any noticeable degree.

(5) Prothrombin deficiency may be present without having made itself apparent until practically uncontrollable bleeding becomes apparent at operation, hence, preparation for transfusion should be a part of the operating room set-up whenever this possibility can not be ruled out, since far too much blood may be lost, although careful hemostasis is practiced as far as recognizable sources of hemorrhage are concerned.

(6) Liver function is undoubtedly impaired in every pronounced case of thyrotoxicosis; it is well, therefore, to carry out some of the well-known liver-tolerance tests in every one of these patients who exhibits a marked case of the disease in either of its two forms. Liver-death is probably more common than usually supposed, hence, is not to be taken lightly as a possibility.

The *preoperative* care of these people may spell the difference between success and failure in the treatment of them. It has been recognized by men who study them that very few enter the hospital in a condition that warrants immediate operation, something which is possible for many patients who are afflicted in other ways. We are able to prepare the diffuse hyperplastic (exophthalmic) patients more quickly and more adequately than the adenomatous ones, since we possess at least two specific remedies for them, while for the last named we are restricted to the general measures which usually benefit both varieties; namely, (1) diet, stressing proteins, at least 115 Gm. daily; (2) rest, apportioned to individual needs; and (3) sedatives in excess of any ordinary need.

We have used iodides in both forms of the disease since Plummer introduced the idea in 1922, though many students of the malady feel that it is not effective in the adenomata. Their value seems to be apparent in the first weeks of their use, which means, usually, that they should be employed only as a preliminary to an operation which has been decided upon. The full effect of iodides can not be secured a second time, and they are surely not indicated for the treatment of a chronic case.

Thiouracil, and similar compounds, are the recent and most effective additions to the list of medicaments which profoundly influence hyperplastic goiter, though they are not equally valuable in the treatment of the adenomata. We have employed them with truly astonishing results, and have been fortunate enough to escape any of the complications or fatalities observed by others, though blood, urine, *etc.*, have been scrutinized at frequent intervals by a capable internist and pathologist at De Paul Hospital. Still, we realize that agranulocytosis, severe anemias and even fatalities have followed their use, and that it is really a question of time until misfortune overtakes any one who employs this useful, though potentially deadly, compound which certainly should be withdrawn at the appearance of trouble.

Thiouracil had not been long in use before operators noted that patients prepared with it bled to a totally unexpected degree; in fact, they seemed to "weep" blood from sources too small for identification. This embarrassing tendency was corrected shortly thereafter by withholding the drug one week previous to operation, then changing to iodine, or to an iodide, with the happy result that no more than the expected amount of bleeding occurred. We have not limited the use of thiouracil to the treatment of diffuse hyperplastic goiter alone, knowing that hyperplasia occurs in thyroid tissue between the nodules of an adenomatous goiter as well as within the adenomata themselves. We have often been gratified by using it thus, though we must admit that its field of greatest usefulness is in the preoperative treatment of the diffuse hyperplastic form of toxic goiter.

We feel that our own *criteria of operability* deserve all the credit during the lengthy periods in which our operative results have been wholly satisfactory. There has been a calamity, sometimes a fatality, every time we have digressed from one or more of them. They are six in number, a certain amount of originality being claimed for the sixth: (1) circulatory; (2) nutritional; (3) central nervous; (4) excretory; (5) metabolic; and (6) breath-holding (voluntary apnea).

The choice of a toxic patient for operation is frequently rendered difficult as far as the heart is concerned by a coincidental *anatomic* lesion of the circulatory system which has no connection with the goiter, toxic or otherwise. After an accurate estimate of the true state of affairs, a prognosis based upon it will do much toward avoidance of the disappointment sure to arise when promised heart improvement fails to follow removal of the goiter which the patient has been told was responsible for all her symptoms. It may occasionally be good judgment to remove half the load by thyroidectomy in many such

TOXIC GOITER

instances, but the patient must be told that chronic vascular trouble remains. *Decompensation* always precludes operation until the patient has had the cardiac mechanism restored; this does not take long in hyperplasia, as a rule, while it may be a very lengthy procedure in toxic adenoma. An old assistant of mine once said of such patients: "Let them do their own dying," a solution which is surely more acceptable than the death which follows operation upon a patient who is not ready for it.

We have seen a few patients who have required a year of treatment before successful operation became possible, while, on the other hand, consultation over a patient dying after thyroidectomy has usually elicited this explanation to me: "We operated because the patient had stopped improving." Such operators are usually men of limited *thyroid* experience. We often have a capable cardiologist examine the patient before selecting a date for operation, though sufficient circulatory improvement should be apparent to any well-trained internist or to a capable surgeon himself. But *remember at all times that the circulatory criteria are the most important of them all.*

Nutritional changes come second on our list. The patient who has lost much weight rather suddenly is never a good risk. Willard Bartlett, Jr. has made the very pertinent observation that loss of weight is not infrequently preceded by a sudden, short, sharp gain, something we have noted too often for it to be mere coincidence, though it seems not to have been widely commented upon.

Central nervous manifestations are surely important criteria, particularly the more severe forms of them. We long ago learned by bitter experience that an insane patient, also one recently so affected (diffuse hyperplasia), invariably dies soon after thyroidectomy.

Excretory phenomena are to be taken seriously, particularly diarrhea and vomiting. We never plan an operation in such cases until at least 50 per cent of the lost weight has been regained, provided, of course, that the other five criteria are satisfactory.

Basal metabolism figures are important only when a comparative study of several observations can be made under similar circumstances, preferably in the hospital under truly *basal* conditions.

Voluntary apnea (our breath-holding test) would seem to be the most convincing of all six criteria, particularly since, to some extent it embraces features of the other five which have preceded it. I first proposed the test at the Dallas meeting of the American Medical Association in 1926, after noting that several patients, thought to be ready for operation, had to be hurriedly returned to bed because they became cyanotic when an inhalation anesthetic was started. Clinical experimentation soon proved that such *unprepared* patients could be identified during breathholding before a *needless* trip to the operating room. The technic of the test, as now used, and its full value, were not realized until Willard Bartlett, Jr., after studying it further, published his article: "Duration of Voluntary Apnea in Thyrotoxicosis: An Index of Stability and Criterion for Operability," Surg. Gynec. and Obst., 63, 576-582, 1936. Two phases of

this problem are now recognized; namely, the importance of the relationship between (1) breath held after inspiration; and (2) breath held after expiration. It is normally held about half as long with an empty chest as it is with chest filled; any great alteration in this 2:1 ratio shows that the patient is *not* prepared for operation, while the same conclusion may be drawn if the breath is not held 40 to 50 seconds after deep inspiration. It may be noted that normal persons hold the breath with full chest from 60 to 100 seconds, while trained athletes extend this to three minutes at times, and there are said to be instances on record of men being saved from drowning after complete submersion for full 15 minutes. A knowledge of the patient's background is, therefore, essential to an adequate interpretation of this test in the individual case.

During and after operation decidedly weighty conclusions must be arrived at and vitally important measures carried out.

The method of anesthetising the patient demands our first attention. Toxic patients should not get enough of a general anesthetic to make them bleed excessively while, on the other hand, the nervous system is unduly sensitive, hence, must be protected to a very definite degree. This we accomplish by the use of a combined nerve block and inhalation. (The method was described in detail in "A Safe and Satisfactory Method of Anesthesia for Toxic Goiter Patients," Willard Bartlett and Willard Bartlett, Jr., Surg., Gynec. and Obstet., 58, 737-740, 1934.)

Our idea is to create skin and fat analgesia by blocking the superficial cervical plexus at the posterior border of the sternomastoid, as had been done by so many others, but to this we add a block of the descending branch of the hypoglossal, thus, securing a like effect on the fasciae and muscles all the way down to the gland itself, which is rendered insensitive by blocking the nerves entering the two upper poles *after* they have been exposed. The entire thyroid region is, thus, rendered devoid of all sensation for an hour or more. All needle pricks, tractive or retractive discomfort are "covered" by a minimum of ethylene gas. This method, which seems to have been widely adopted, is so successful that we frequently employ it on *nontoxic* patients, omitting the use of a general anesthetic entirely.

A second therapeutic measure carried out by us *during operation* is the intravenous introduction of 200 cc. of 25 per cent hypertonic dextrose, based on the observation that patients who die from goiter operation present the picture of cerebral edema, which, quite naturally, suggests the desirability of the hypertonic treatment.

Our third suggestion for the period of the operation, always a vital time, has to do with the excessive *use of oxygen*, whether or not it seems particularly indicated; this seems to come as a matter of course in view of the anoxia on exertion which these patients all show when first seen.

A fourth consideration has to do with *sodium iodide*, one or two ampoules of which are added to the intravenous injection at the table. This is particu-

TOXIC GOITER

larly valuable for the patient who has been prepared by administration of thiouracil, and who tends to bleed without an iodide.

In the fifth place, we add a large dose of *vitamin-K* to the already mentioned intravenous iodide, though three daily administrations of it have been carried out previously during the late preparatory period.

We realize the need of fluid for all patients, hence, the *hypodermic* introduction of 2,000 cc. of 5 per cent dextrose is started after the patient is returned to bed, but so slowly absorbed as not to destroy the effect of the *hypertonic* solution which has preceded it.

Another consideration has to do with the extreme protein need of the toxic goiter patient. We tried to meet this need by feeding during the pre-operative period, so it seems logical now, during the period of extreme stress, to inject under the skin one or two ampoules of *amino-acids* (Stearns), meeting in this way any added acute load.

Immediately following the operation we give *sedatives*, enough to insure perfect quiet on the patient's part, though less than the expected degree of pain follows a well-carried-out nerve block.

When temperature rises to 102°F. in the early postoperative course we have four ice-bags applied, one to the forehead, one to the precordial region, and one to the inner aspect of each thigh. The patient is closely watched and the bags quickly removed if the body temperature is forced to a subnormal degree.

Fluid intake, by whatever route, is strictly limited, as has been mentioned, during the first few hours while cerebral and other edemas are considered possible.

Propyl thiouracil would seem to be *comparatively* harmless, and we have proved by their use in thousands of cases, that the six criteria of operability we are presenting, cover all essential risks, hence, this combination should reduce the mortality of thyroidectomy to almost the vanishing point. This is a prediction in which we may well take pride when it is remembered in comparison that Dr. C. H. Mayo, the incomparable pioneer in the field of toxic goiter a half century ago, experienced a mortality of 25 per cent in his first short series of the then little understood toxic patients, as he told me in January, 1902, when I first visited him and his equally promising brother who were both then new to fame.

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THE USE OF THIOURACIL, THIOBARBITAL AND PROPYL THIOURACIL IN PATIENTS WITH HYPERTHYROIDISM*

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THE USE OF AGENTS capable of bringing to normal the elevated basal metabolic rate of hyperthyroidism has greatly reduced the complications of this abnormal metabolic state. Astwood, to whom we are all indebted for his work on these drugs, has proposed three different drugs of the thiourea group for employment in this disease, first thiouracil, then thiobarbital and now propyl thiouracil.

As is the case with all new agents, particularly while they are in the trial stage and experience with them is being gained, many premature, over-optimistic and conflicting statements are made about them. It is for this reason we think that it is important for anyone who has had a large experience with them to keep reporting their results for others while they are gaining their own experience with these agents. These drugs are extremely powerful and effective and because of this powerful effect on inhibiting the synthesis of thyroxin they have in certain cases an equally powerful capacity to depress bone marrow function and produce agranulocytosis which can and already have brought about a considerable number of avoidable fatalities. We have used one or more of these agents over a period of three and one-half years and have now prepared 660 patients with various types of hyperthyroidism for thyroidectomy, and in addition have employed these agents in a series of 21 cases over a long period of time to determine whether they can be used as a substitute for operation. We would like to propose a series of pertinent questions concerning these drugs and attempt to answer them from our experience which is now large enough and long enough to permit answers with a reasonable assurance of their soundness.

HOW DO THESE DRUGS ACT TO REDUCE THE BASAL METABOLIC RATE?

In attempting to answer this question, one is able to state only the results obtained by the use of these drugs. We know that if given in an adequate dose they completely halt the synthesis of inorganic iodine into diiodotyrosine on into thyroxin, as is proven by the drop in the protein-bound iodine. The basal metabolic rate drops and if the agent is continued long enough, myxedema results and is maintained as long as the drug is given.

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

HYPERTHYROIDISM

Unlike iodine which produces prompt and striking histologic change in the thyroid gland, which at least is relatively proportionate to the change in the clinical and metabolic picture, these three agents, thiouracil, thiobarbital and propyl thiouracil, produce even more striking effects upon the clinical and metabolic picture but with practically no change in the histologic picture. Since it is true that the function of the thyroid cell by which iodine is synthesized into thyroxin is not demonstrable by histologic examination, so the method by which thiourea agents stop the synthesis of thyroxin is as yet not satisfactorily explained. It is important to have in mind, as relates to the question of whether or not these drugs will prove to be a complete or partial substitute for subtotal thyroidectomy, that the pathologic histology (hyperplasia) which originally brings about hyperthyroidism is still present even after these drugs have reduced the basal metabolic rate to normal, and that on stopping these agents the necessary factor for the restoration of an elevated metabolism (hyperplasia) is still present.

WILL THESE AGENTS ALWAYS BRING THE METABOLISM TO NORMAL?

Since many patients become iodine-fast or iodine-resistant, the question has often been asked as to whether or not this condition arises in patients with hyperthyroidism while being treated with these drugs, thiouracil, thiobarbital or propyl thiouracil. In spite of the fact that we have been told by others

TABLE I
COMPARATIVE DAILY DOSAGE OF ANTITHYROID DRUGS

Drug	Daily Dosage, Mg.
Thiouracil	600
Thiobarbital.....	50
Propyl thiouracil	200

that this occurs, it has not been our experience. There has been no patient in whom, if given one of these drugs in a large enough dose over a long enough period of time, if not compelled to stop it because of a complication, we have not been able to bring the metabolic rate to normal.

To discuss dosage first and length of time the drug needs to be administered afterward (Table I), we believe that the drugs thiouracil and thiobarbital which have been employed over the longest period of time have had their effective doses well established—thiouracil 0.6 Gm. and thiobarbital 50 mg. daily. The drug which we now employ to the exclusion of the other two, propyl thiouracil, coming as it has after the other two, has only recently had its dosage in comparable effectiveness established. The factor of inadequate dosage was early responsible for the poor response of some of our patients, and because of the inadequate doses administered, may be responsible for the assumption that there are no complications from the use of propyl thiouracil. The dose which was originally suggested, 75 to 125 mg. daily, in preparing patients with hyperthyroidism for surgery was entirely inadequate

to prepare these patients and when they came to surgery they were not entirely free from hyperthyroidism. It was not until the dosage was increased to 200 to 225 mg. daily that full control of hyperthyroidism was accomplished.

Since most of the patients to whom we administer these metabolism-depressing agents are receiving it in preparation for thyroidectomy, it is important to be able to estimate with reasonable accuracy when their metabolic rate will reach normal and when they will be ready for operation. With the shortage of hospital beds and since many of these patients live at a considerable distance from the clinic, we must be able with reasonable sureness to predict when the patient is to return to the hospital, free from toxic symptoms and with a normal or practically normal basal metabolic rate, for subtotal thyroidectomy.

This prediction is based upon what are now some quite soundly established facts. When a patient is upon an adequate dose of thiouracil, thiobarbital or propyl thiouracil, thyroxin will no longer be manufactured, and although these drugs will abolish the synthesis of thyroxin, they have no effect whatever upon the thyroxin which is already synthesized and stored. From this it can be seen that the time required to bring the elevated metabolic rate to normal depends upon the amount of already synthesized thyroxin in storage.

The time required to bring the elevated basal metabolic rate to normal, in our experience, is determined from the following factors: the type of thyroid disease—primary hyperthyroidism or adenomatous goiter; the duration of the disease and whether or not iodine had been taken previously. Patients with primary hyperthyroidism who have had the disease nine months, or less, and have not taken iodine have a daily drop of 1.3 in the basal metabolic rate; if iodine had previously been taken, the drop is 1 per day. If the hyperthyroidism is over one year in duration, irrespective of iodine, the drop is 1 per day.

Patients with toxic adenomatous goiters, particularly those who have been treated with iodine before preoperative preparation, require a much longer period of time to restore the basal metabolic rate to normal because these glands, with their large store of thyroxin-laden colloid, have greater reserves of thyroxin. In this type there will be a drop in the metabolic rate of approximately 0.5 per day. The longest time we have given these agents to bring the basal metabolism to normal was 180 days in a patient with a large, toxic adenomatous goiter who had been receiving iodine for a long period of time before preparation for surgery. Treatment to be satisfactory must be individualized.

WHICH OF THE THREE DRUGS, THIOURACIL, THIOBARBITAL OR PROPYL
THIOURACIL, IS THE MOST SATISFACTORY AND WHY?

Now that an adequate dose of propyl thiouracil has been established, it can be said that all three of these agents are equally effective in lowering the basal metabolic rate. Each reduces the metabolism as positively and with

HYPERTHYROIDISM

equal promptness, so the choice of agent must be made solely on the basis of the percentage of complications associated with each agent and the percentage of cases in which it is necessary to abandon the administration of the drug (Table II). Of the three agents, thiobarbital is the most dangerous, having an incidence of complications of 28 per cent. Thiouracil is next in risk of complications, the incidence being 9 per cent, and propyl thiouracil is by far the safest, 2 per cent.

Because of the equal effectiveness and low incidence of complications with propyl thiouracil, we believe that, with one exception, the use of thiouracil and thiobarbital, with their high incidence of complications, should be abandoned and all patients treated with propyl thiouracil. The one exception to

TABLE II
INCIDENCE OF REACTIONS TO ANTITHYROID DRUGS
(Operated Cases)

Drug	Patients Treated, Number	Reactions,	
		Number	Per Cent
Thiouracil	381	34	9
Thiobarbital	28	8	28
Propyl thiouracil	260	6	2
Total	660*		

* Nine patients received both thiouracil and thiobarbital.

TABLE III
TYPES OF REACTION TO ANTITHYROID DRUGS

Thiouracil	Thiobarbital	Propyl thiouracil
White blood cell depression	White blood cell depression	White blood cell depression
Fever	Fever	Fever
Skin rash		
Swollen salivary glands		
Edema of skin		
One death—agranulocytosis	No deaths	No deaths

this statement is the occasional case under treatment with propyl thiouracil in which a complication arises; one may substitute thiouracil for propyl thiouracil and finish the preparation without further complications. Thiobarbital, with its high percentage of serious complications, more than one in four, should be abandoned.

WHAT ARE THE COMPLICATIONS, HOW ARE THEY TREATED, AND WHEN IS THE DRUG TO BE STOPPED?

The complications (Table III) associated with the use of these drugs are, in our experience, largely associated with the first two drugs, thiouracil and thiobarbital, and are depression of the white blood cells, skin eruption, fever reactions (associated with the generalized symptoms of joint pains and

backache), and salivary gland enlargement. One case of pancreatic enlargement has been reported which produced severe pain and a palpable tumor which required operation. With the known capacity for these drugs to produce pancreatic hyperplasia it is well to have in mind that such a complication might occur.

In our experience with propyl thiouracil in preparing 260 patients for surgery there have been but two types of complications, and those in limited numbers; one patient had fever and five patients showed depression of the white blood cells. In four of these five patients the depression was mild and in one it was severe, with agranulocytosis, demonstrating the relative safety and desirability of this drug as compared with thiouracil and thiobarbital.

Since the fatalities which have occurred during the administration of these drugs have been solely in those patients having bone marrow depression (leukopenia and neutropenia), two questions naturally arise and require answers: how often should white and differential counts be made and at what lowered levels of total and differential white counts is it desirable to omit treatment with these drugs? Also, what are the causes of the fatalities in the patients with agranulocytosis produced by these drugs and what treatment is advisable? If reports of the white and differential counts were available every day, one would have safe control of these patients, but this is impossible and hardly necessary; a count every 10 to 14 days is all that seems necessary. When the white blood count falls as low as 4,500 and when the granulocytes are found to be reduced to 45 per cent, further administration of these agents should be discontinued or carefully scrutinized.

Fatalities in the group of patients with low leukocyte and granulocyte counts are the result of the occurrence of infections of a severe character and serious nature at a time when the depressed bone marrow is unable to produce an adequate number of granulocytes with which to deal effectively with the infections. As a result of having dealt with a number of these agranulocytic states, in which early in our experience one fatality occurred, we have learned that penicillin is the sole agent upon which one can place dependence, acting as it does to control the infection, while by omission of the drug, thiouracil thiobarbital or propyl thiouracil, the bone marrow is permitted to regain its function. Because of this we urgently stress to patients the necessity of reporting promptly the development of sore throat or any other type of infection. We have seen no benefit from the use of vitamin B₆ (pyridoxine) or the use of liver extract in patients with agranulocytic states resulting from one of these three drugs. At the earliest possible discovery of an agranulocytic state, the omission of the drug is essential, with the prompt employment of large doses of penicillin intramuscularly and by throat spray.

SURGICAL DISADVANTAGES OF THE THIOUREA GROUP OF DRUGS

Since this group of drugs, while lowering the basal metabolic rate to normal, still leaves the thyroid gland in a state of hyperplasia, it is obvious that, as was the complaint of every surgeon who operated upon hyperthyroid

HYPERTHYROIDISM

patients prepared solely with one of these drugs in the presence of such hyperplasia, operating conditions would be unfavorable, which is distinctly an understatement of fact—they were, in fact, almost impossible. Until we had learned how to bring about involution of these hyperplastic glands with iodine we know of no operation which was more technically distressing than that of subtotal thyroidectomy in a patient with primary hyperthyroidism whose basal metabolic rate had been brought to normal. All the advantages of operating upon a patient freed from his toxicity were more than offset by the technical difficulties encountered—friability of the gland, uncontrollable bleeding and inability to obtain satisfactory anatomic exposure. By the plan of omitting the thiouracil or propyl thiouracil for the last week of treatment and administering iodine for the last three weeks of treatment, these disadvantages are completely overcome.

Except in those patients with dangerous states of thyroid toxicity (crisis) or with dangerous complications (cardiac failure) an estimate is made on the basis of the data already discussed of the period of time necessary to administer propyl thiouracil in order to bring the basal metabolic rate to normal. This period is divided into weeks and the patient given propyl thiouracil, 100 mg. every 12 hours, up to the last week, during which week the drug is omitted. It is omitted for the last week because its effect will be maintained for that period of time and, more important, we have seen agranulocytic effects appear up to a week after the withdrawal of the drug, and we wish to avoid even the remote chance of such an occurrence at the time the patient is ready for operation or immediately after the surgical procedure. We had thought it undesirable to combine the administration of these thiourea drugs with the simultaneous administration of iodine because it was feared that iodine would lessen their metabolism-lowering effectiveness and prolong the period of time necessary to bring the metabolism to normal. The latter assumption has not proved to be true, as shown by recent experiences, and now the plan of therapy has undergone modification in that, in addition to the two groups of cases already cited, patients in thyroid crises and patients with severe hyperthyroidism and heart failure, all patients with primary hyperthyroidism now receive propyl thiouracil and iodine simultaneously. The addition of iodine has prolonged the response to therapy of the group who had a 1.3 drop in the basal metabolic rate, now, the response of all patients with primary hyperthyroidism is a drop of 1 in the basal metabolic rate a day. This modification was brought about by the fact that we have seen patients, especially those in dangerous states of hyperthyroidism, get worse during their first week of treatment when on thiouracil or propyl thiouracil alone. Although we know the metabolism-lowering effect of iodine upon the thyroid is ultimately less positive and dramatic, its immediate effect is more prompt. The two drugs are now given from the first day of treatment and continued in combination throughout the entire period of preparing these patients for operation. It should be mentioned that patients with adenomatous goiters do not require iodine therapy.

HOW LOW SHOULD THE METABOLISM BE REDUCED?

While it is not of great importance, it is of value to call attention to the fact that occasionally patients who have been prepared for surgery over a considerable period of time with these drugs may report for operation with low metabolic rates and in varying degrees of myxedema. Two features of this state and their relationship to possible postoperative difficulties are worth keeping in mind; one is that every patient upon whom a subtotal thyroidectomy is done will have varying degrees of postoperative edema of the larynx which, if superimposed upon some myxedematous infiltration of the larynx and cords which occurs in patients with marked hypothyroid states, will result in difficulty with breathing owing to a temporarily inadequate airway. It is also well to call attention to the fact that patients in these hypothyroid states are particularly sensitive to morphine, causing a depression of the respiratory rate, and that the combination of these two undesirable states can and has made it necessary for us in one case to perform a tracheotomy; had we operated upon this patient in a normal instead of a minus metabolic state, a tracheotomy would have been avoided.

WHICH PATIENTS SHOULD BE TREATED PREOPERATIVELY WITH THESE DRUGS?

Our early preoperative use of these drugs was limited to patients having severe hyperthyroidism (35 per cent of the total hyperthyroid patients), many of whom had complicating diseases. More recently, because of the lessened incidence of reactions to propyl thiouracil, an increasing number of patients are now receiving this type of preoperative therapy, and in the future perhaps most patients will be so treated. We realize, however, that Lugol's solution alone is very effective as a preoperative measure in patients with mild primary hyperthyroidism. A high percentage of patients with adenomatous goiters has from the onset been prepared with these drugs since patients with this type of hyperthyroidism make up a large percentage of the increased risk cases and little or no benefit is to be expected in these cases from the administration of Lugol's solution. As many patients must now wait for weeks before a hospital bed is procured, it seems wise to give treatment even to the less toxic patients so that on their admission to the hospital for thyroidectomy the hyperthyroidism is fully controlled and risk of thyroidectomy abolished.

Patients with severe, complicated hyperthyroidism are bound to benefit most from therapy since, irrespective of the type of complication, these patients can now be restored to a no-risk status. There were 115 thyrocardiacs among the 660 patients treated. Before the use of these new drugs, thyroidectomy was undertaken in thyrocardiac patients with great risk, the operative mortality being 6.7 per cent. There was but one death (the only one in the 660 patients—see Table IV) on the second postoperative day as a result of coronary disease. This patient appeared well but died suddenly after having recovered from the immediate effects of the operation. This one death evi-

HYPERTHYROIDISM

dences a great saving in life when compared with the estimated mortality in the past of eight deaths in a similar group of thyrocardiacs.

Eight patients were in the various trimesters of pregnancy and in these patients preoperative treatment was carried out in the usual way without concern for the pregnancy. All had thyroidectomy without incident and the pregnancy proceeded normally with each patient delivering a normal baby.

There were ten children under the age of 15, all with severe primary hyperthyroidism, who received treatment, giving full doses of the antithyroid drug (200 mg.), identical to the dosage employed in the older patients. The response to treatment followed the usual predictable pattern until there was full control of hyperthyroidism, at which time subtotal thyroidectomy was undertaken, without reaction.

TABLE IV
OPERATIVE MORTALITY—THYROIDECTOMY
(Preoperative Antithyroid Treatment)

Total number of patients.....	660
Postoperative deaths (2nd day postoperatively, coronary infarct).....	1
Percentage mortality.....	0.15%

There were four patients with psychoses (either primary or secondary to hyperthyroidism) who received treatment with striking ease and great benefit. These patients had mental conditions which would seem to contraindicate thyroidectomy, but improvement was sufficient in all cases to permit thyroidectomy under ideal conditions.

The 26 patients who had associated diabetes were also aided by this treatment. In some the diabetes became latent and, of those requiring insulin, the amount of insulin was reduced and the glycosuria was less difficult to control before and immediately after thyroidectomy.

The use of thiouracil, thiobarbital and propyl thiouracil has permitted a change in the approach to the treatment of diseases complicating hyperthyroidism. Before the era of these drugs the policy was to treat the hyperthyroid condition first and then the complicating disease. Now the hyperthyroidism is placed under control and then, if necessary, the complicating disease is treated, followed by thyroidectomy. One patient with frequent, recurring gallstone colic and one patient with thrombocytopenia were treated in this way. The latter case would have represented a serious problem since splenectomy, without control of the hyperthyroidism, would have been done with great risk and the danger of doing a thyroidectomy in the presence of extremely low platelets would have been equally great.

WILL THESE DRUGS BE A SUBSTITUTE FOR THYROIDECTOMY?

As already mentioned, the microscopic studies of the thyroid tissue removed at operation in patients receiving these drugs without the simultaneous use of iodine did not reveal regressive changes but there was a tendency toward increased hyperplasia of the thyroid gland. It was, therefore, con-

cluded that since the thyroid gland remained hyperplastic and, as observed clinically, the thyroid did not decrease in size, permanent cure of hyperthyroidism is not to be expected from the administration of these agents. We have had prolonged experience with 21 patients with primary hyperthyroidism who received thiouracil, until the hyperthyroidism was controlled, and observations were continued after withdrawal of the agent to determine their clinical course. All the patients had primary hyperthyroidism; 11 had recurrent primary hyperthyroidism. Treatment with thiouracil was begun in all patients with a dose of 0.6 Gm. daily; in some it was continued at this dosage up to the time of its withdrawal and in others the dose was gradually decreased as improvement was noted. Thiouracil was administered for as long as 20 months in one case. The shortest period of treatment was two months. After the withdrawal of the drug, eight patients have remained in remission and 13 patients have suffered a relapse of hyperthyroidism.

An analysis of the two groups of patients, those with relapse and those remaining in remission, revealed that the duration of administration of thiouracil after restoration of the basal metabolic rate to normal was not a factor in determining the duration of remission that followed since prolonged remissions occurred after short therapy and prompt relapse was observed after prolonged treatment. The eight patients still in remission had mild hyperthyroidism, with only slight enlargement of the thyroid gland, or small recurrent remnants. Those who had relapses had moderate to severe hyperthyroidism with large thyroid glands or large recurrent remnants. These observations indicate that thiouracil or its allied drugs have little to offer from a curative standpoint in cases of severe hyperthyroidism but that in mild hyperthyroidism with slight thyroid enlargement they may cause a remission similar to that which has been observed following the administration of Lugol's solution, or remissions which at times occur spontaneously. Since the basic etiologic factor which causes hyperthyroidism is still undetermined and as thiouracil probably does not affect this factor along with its known effect on the thyroid cells (hyperplasia), it can hardly be expected that thiouracil produces more than a temporary remission of the disease. Since the risk of thyroidectomy is now so small, one death in 660 cases, as there is always a risk of developing sensitivity to the drug in spite of continuous observation, and as no great promise of permanent cure from these drugs can be held out for patients with severe degrees of hyperthyroidism, we believe that thyroidectomy following proper preparation is the treatment of choice in hyperthyroidism.

CONCLUSIONS

Experience with the preoperative use of thiouracil, thiobarbital and propyl thiouracil in 660 cases of hyperthyroidism during the last three and one-half years has permitted answers to certain questions regarding these drugs. These drugs act by preventing the synthesis of an active thyroid hormone and by so doing lead to an increase in hyperplasia of the thyroid gland, an hyperplasia similar to, but greater than, that in primary hyperthyroidism. If these drugs are

HYPERTHYROIDISM

used in adequate doses over a sufficient length of time no patient will fail to obtain restoration of the basal metabolic rate to a normal level. The comparative dose of thiouracil, thiobarbital and propyl thiouracil is 600 mg., 50 mg. and 200 mg., respectively.

Since the percentage of reactions is mine for thiouracil, 28 for thiobarbital and two for propyl thiouracil, the last named agent is the drug of choice. Since propyl thiouracil may also cause depressive changes in the white blood cells, its administration must be carefully followed with white and differential blood counts made every 10 to 14 days during treatment. The treatment of agranulocytosis consists of the early administration, intramuscularly and by nasal and throat spray, of adequate doses of penicillin.

The time required to restore the basal metabolic rate to normal for complete relief of all hyperthyroid signs and symptoms can be estimated from the type of hyperthyroidism, primary or adenomatous, duration of hyperthyroidism, whether iodine has previously been received, and the size of the thyroid gland. Rapid response occurred in patients with primary hyperthyroidism of short duration without previous administration of iodine (1.3 per cent drop in the basal metabolic rate per day), and slow response occurred in patients with adenomatous goiter when iodine had been administered previously (0.5 per cent drop in the metabolic rate daily). From this information, an individualized program of adequate treatment can be outlined and hospital reservations can be made in advance. Over-treatment with these agents must be avoided since myxedema will result which may increase the surgical risk.

The surgical disadvantage of these drugs in cases of primary hyperthyroidism—increase in vascularity and, therefore, great technical difficulty in carrying out the thyroidectomy—has now been overcome by the use of iodine. Initially, iodine was given during the three-week period before operation but now both drugs are given simultaneously from the start of treatment. The time required for control of hyperthyroidism has not been prolonged and with the rapid immediate benefit from iodine, patients seem to show improvement much sooner than on the plan of giving thiouracil only at the beginning of treatment and adding iodine at the end of therapy.

Initially, only severely hyperthyroid patients were treated preoperatively with these drugs, but now since propyl thiouracil, which has such a low sensitivity rate, is available, we are preparing an increasing number of hyperthyroid patients with this drug. Patients with very mild hyperthyroidism, however, are still prepared with Lugol's solution alone.

These antithyroid drugs do have the capacity to produce prolonged remissions of mild primary hyperthyroidism, as does iodine at times, but little hope can be held for a permanent remission in patients with severe primary hyperthyroidism with a large gland. Since the mortality of thyroidectomy is now almost *nil*, surgical removal after proper preoperative treatment seems to be the treatment of choice for hyperthyroidism.

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USE OF THYROID EXTRACT WITH THIOURACIL IN THE PREPARATION OF THE THYROTOXIC PATIENT*

A PRELIMINARY REPORT

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THE INTRODUCTION of thiouracil placed in our hands a valuable drug for the treatment of the thyrotoxic patient. Opinions still differ as to its usefulness in definitive therapy but its advantages in the preparation of these patients for operation are now generally recognized. However, it soon became evident that the drug has certain disadvantages. Chief among these are the length of time required to prepare the patient,¹ the dangerous side-effects sometimes encountered and, lastly, vascularization, hypertrophy and hyperplasia of the gland² which make thyroidectomy technically difficult. This is a preliminary report of an attempt to prevent these undesirable changes in the gland itself and, thus, reduce the technical difficulties during the operation. It is also hoped that this method will shorten the time required for preoperative preparation of the patient.

The hyperplastic changes produced by the administration of thiouracil may have more than one disadvantage. Not infrequently, the size of the gland increases considerably during this therapy and the microscopic appearance is such that at times the pathologist has difficulty in differentiating it from malignancy. All of which has led Hinton and Lord³ to warn against the use of thiouracil in nodular goiter because of its possible carcinogenic effect, where malignancies already tend to occur. One investigator⁴ has been able to produce invasive tumors in animals by giving thiouracil and a carcinogen, but no such results were obtained when one was given without the other.

The increased vascularity and friability brought about by thiouracil was a distinct disadvantage to the surgeon and means were sought to prevent this effect from the drug. As a result, at some stage of preparation of the patient iodine is now given because of its involutionary effect. One group of investigators⁵ believes that iodine can diminish the hyperplasia of the secretory cells even though given at the same time as thiouracil. It is the consensus, however, that under such circumstances the response is delayed and preparation somewhat prolonged. In my experience thyroid glands prepared in this way have been only slightly less vascular than those treated with thiouracil alone, unless the preparation is thorough and prolonged. This difficulty can be remedied if iodine is given ten days or two weeks after thiouracil has been

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THE THYROTOXIC PATIENT

discontinued. This produces a satisfactory gland but adds to the time required for preparing the patient for operation.

The mechanism by which hyperplasia is produced by thiouracil and other goitrogens is now moderately well understood. In experimental animals this effect of the drug can be abolished by hypophysectomy or the administration of thyroxin.^{6, 7, 8} Iodine does not produce the same result.^{6, 7, 8} For this reason, it is postulated that the circulating thyroid hormone acts as an inhibitor on the pituitary, particularly, as far as the production of the thyrotropic factor. If a goitrogen is administered, a prompt fall in the circulating thyroid hormone ensues; this removes its inhibitory influence on the pituitary gland, which, in turn, responds by increased production of thyrotropic hormone.^{2, 9} The latter is believed responsible for the hyperplastic changes in the thyroid gland (Fig. 1).

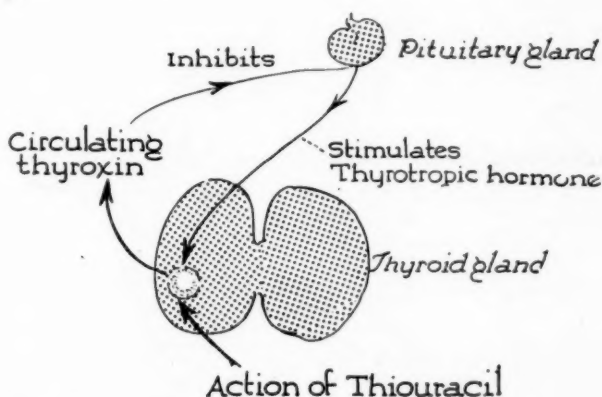


FIG. 1.—Schematic representation of the probable mechanism of the production of hyperplastic changes in the thyroid gland following the administration of thiouracil.

On the basis of the reasoning in the preceding paragraph, thyrotoxic patients were prepared for operation by the administration of both thiouracil and desiccated thyroid. Williams and Clute¹⁰ instituted this regimen in a few patients but apparently it was directed at the exophthalmus. Palmer¹¹ also mentions using thyroid extracts to prevent hyperplasia but gives no results except to state that the administration of thyroxin was found to have no appreciable inhibiting effect on the action of thiouracil in lowering the metabolic rate.

Six patients with classical signs of exophthalmic goiter were prepared for operation by the administration of thiouracil and desiccated thyroid extract. Considerable loss of weight, tachycardia and elevated metabolic rates were evident in all six patients. The average basal metabolic rate on admission for these patients was plus 58. Varying degrees of enlargement of the thyroid gland were present. Thiouracil (0.2 Gm.) was administered three times a day to all patients, and with each dose desiccated thyroid (1 gr.) was also given. In most instances the medications were started on the same day, but in no

case was administration of the thyroid begun longer than one week following the initial dose of thiouracil. These patients received no iodine, as such, at any time.

The preoperative course in each case was satisfactory and was thought to be no different from that of patients who received thiouracil and iodine. A possible exception to this statement was the response shown by the pulse rate but this was hardly significant enough to warrant a definite conclusion except in one instance. This was a middle-aged woman who responded satisfactorily, but the pulse rate decreased more slowly than usual, and following operation pronounced tachycardia persisted for two days. In some instances

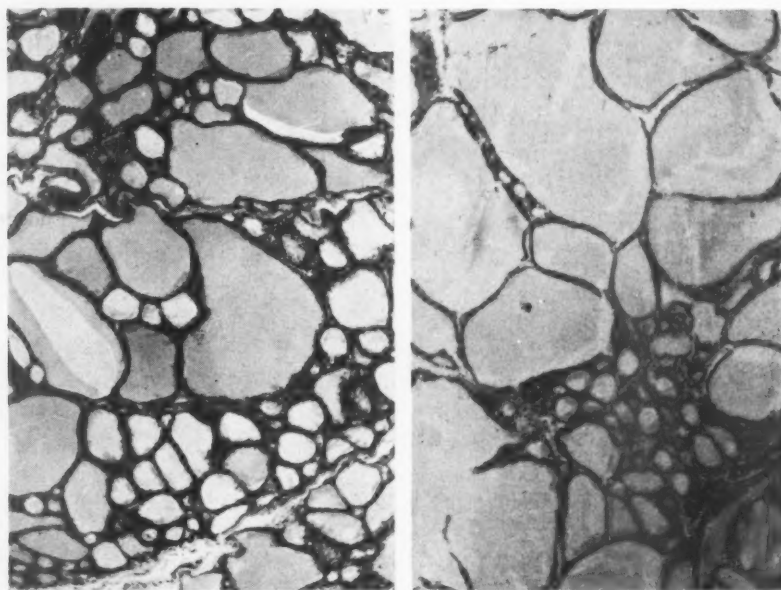


FIG. 2.—Photomicrograph of glands removed from two of the patients treated with both thiouracil and desiccated thyroid, but no iodine. Note the large amount of colloid. (x 90)

the thyroid gland became much smaller in size. The average number of days required for preparing these patients was 39.

Thyroidectomy was performed upon every patient. The technical difficulties of the operations were not great. About half of the glands seemed to be no more vascular than those treated in the conventional way with thiouracil and iodine. In the other three cases the gland was perhaps a little more vascular but this was not as great as in those patients whom we prepared by giving thiouracil and iodine at the same time. The postoperative course was uneventful except in the one patient referred to earlier.

Microscopic examination of the removed glands showed satisfactory involution in all (Fig. 2). There was a noticeable increase in colloid, definitely more than is found in untreated exophthalmic goiter, which is usually more

THE THYROTOXIC PATIENT

than is found after treatment with thiouracil. The height of the epithelium was never great, although in some instances there were patches of residual hyperplasia sometimes involving only a small tuft in the acinus. It was felt that with more prolonged treatment even this residual hyperplasia would have disappeared.

SUMMARY

Desiccated thyroid was given in conjunction with thiouracil to six patients with exophthalmic goiter, in an attempt to bring about involution of the gland while the patient was being prepared for operation. The pre-operative and postoperative courses were like those noted when thiouracil and iodine are used, except for tachycardia in one patient. Microscopic examination of the removed tissue showed satisfactory involution in all cases. The vascularity of the glands presented no technical problem for the surgeon but the glands were probably not quite as avascular as those treated with thiouracil and then iodine. It is believed that the use of desiccated thyroid offers a satisfactory adjunctive method of preparing thyrotoxic patients for operation.

REFERENCES

- ¹ Astwood, E. B.: Thiouracil Treatment in Hyperthyroidism. *J. Clin. Endocrinology*, **4**, 229, 1944.
- ² Rawson, R. W., Evans, R. D., Means, J. H., Peacock, W. C., Herman, J., and Cor-tell, R. E.: Action of Thiouracil upon the Thyroid Gland in Graves' Disease. *J. Clin. Endocrinology*, **4**, 1, 1944.
- ³ Hinton, J. W., and Lord, J. W., Jr.: Is Surgery Indicated in all Cases of Nodular Goiter Toxic and Nontoxic? *J. A. M. A.*, **129**, 605, 1945.
- ⁴ Bielschowsky, F.: Distant Tumours Produced by 2-amino and 2-acetyl-amino-fluorene. *Brit. J. Exper. Path.*, **25**, 1, 1944.
- ⁵ Rawson, R. W., Moore, F. D., Peacock, W., Means, J. H., Cope, O., and Riddell, Charlotte: Effect of Iodine on the Thyroid Gland in Graves' Disease when given in Conjunction with Thiouracil. *J. Clin. Investigation*, **24**, 869, 1945.
- ⁶ Higgins, G. M., and Ingle, D. J.: The Relation of the Hypophysis to Certain Changes Induced in the Rat by the Goitrogen, Promizole. *Endocrinology*, **38**, 110, 1946.
- ⁷ MacKenzie, C. G., and MacKenzie, Julia B.: Effect of Sulfonamides and Thioureas on the Thyroid Gland and Basal Metabolism. *Endocrinology*, **32**, 185, 1943.
- ⁸ Astwood, E. B., Sullivan, J., Bissell, A., and Tyslowitz, R.: Action of Certain Sulfonamides and of Thiourea upon the Function of the Thyroid Gland of the Rat. *Endocrinology*, **32**, 210, 1943.
- ⁹ Gordon, A. S., Goldsmith, E. D., and Charipper, H. A.: Thyrotropic Hormone Content of the Blood Sera and Pituitary Glands of Thiourea-, Sulfadiazine-treated and Thyroidectomized Rats. *Endocrinology*, **36**, 53, 1945.
- ¹⁰ Williams, R. H., and Clute, H. M.: Thiouracil in the Treatment of Thyrotoxicosis. *New England J. Med.*, **230**, 657, 1944.
- ¹¹ Palmer, M. V.: Hyperthyroidism and Thiouracil. *Ann. Int. Med.*, **22**, 335, 1945.

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DISCUSSION.—DR. ELMER C. BARTELS, Boston, Mass.: Doctor Lahey has asked me to limit my discussion to the impressions of the internist regarding the use of these drugs as permanent medical treatment. The objection to their use should not be based solely on the grounds of possible reactions which may follow their use, since I expect that some new drug will be discovered which will have a low toxic incidence, which

requirement propyl thiouracil very nearly fulfills. The objections seem to be more fundamental and can be considered from the pathologic and clinical standpoints. I think there are three or four objections pathologically. First, patients with adenomatous goiters should not be treated with these substances over long periods of time, since there is definite danger of malignant degeneration. Second, in primary hyperthyroidism the hyperplasia which is initially present is increased, so that when the drug is withdrawn the stage is set for a return of hyperthyroidism. Third, the thyroid gland does not decrease in size, although some observers have thought that it does. Certainly, the bruit and thrill remain, and in some instances become accentuated. Fourth, malignant changes might develop in the primary hyperplastic gland, although this, at the present time, is still under discussion. From the clinical standpoint, sustained remission after withdrawal of thiouracil treatment has not been very promising in our experience. Thirteen patients were treated over varying periods of time, over a year in some instances. Irrespective of the length of time, all patients had relapses of the disease. They all had severe hyperthyroidism, with large thyroid glands or large thyroid remnants. Eight patients after withdrawal of treatment have had remissions irrespective of duration of treatment. All had mild hyperthyroidism, with small thyroid glands or small remnants. Most of these patients would probably have reacted similarly to Lugol's solution.

We are at the present time seeing an increased number of patients suffering from relapse of hyperthyroidism to whom thiouracil had been administered before they came to the clinic. Some of these patients could ill afford the effect of delay and uncertainty of thiouracil as a medical therapy and the visceral strain which accompanied recurrent hyperthyroidism. We believe our responsibility to the hyperthyroid patient is one of restoration to health in the shortest possible time and with the least risk, and that these antithyroid drugs, when properly used, with subsequent thyroidectomy, give the patient the best chance of obtaining this end.

DR. ROBERT L. PAYNE, Norfolk, Va.: A single surgeon operating in a small community cannot enjoy the privileged experiences of a large clinic. Yet I have been using thiouracil and propyl thiouracil for about two and one-half years.

Last December I reported the result of 45 cases treated with thiouracil, in five of whom leukopenia developed and was treated by withdrawal of the drug and administration of penicillin. All recovered. We continued the use of thiouracil until about six months ago when propyl thiouracil became available. We have now used this in about 15 cases and have seen no toxic effects. Interestingly enough, some patients who showed leukopenia from thiouracil before we got propyl thiouracil, had no bone marrow reaction whatsoever after being put upon propyl thiouracil.

I particularly arose to take part in this discussion because the carcinogenic effects of thiouracil have been pointed out and, as Doctor Bartels said, these drugs should not be used in the nodular type of goiter lest carcinoma be produced in the adenoma. I have had one case whom I treated with thiouracil that showed carcinoma. Stained sections of tissue were submitted to several outstanding pathologists of this country and all unanimously agreed that the sections showed carcinoma. A report of this case was written up carefully and conservatively, with no implication that the drug produced the carcinoma. The report of the case, together with photomicrographs, was submitted to one of our best surgical journals, and publication of the report was declined. Excerpts of the opinions of five of the editorial board were sent to me, and I agree with them entirely. Their opinions were based on the supposition that the report would create a bad impression and deter the use of the drug in toxic hyperthyroidism. Up to that time there had been no cases reported in the literature following the use of thiouracil. There was one case reported in a discussion on this subject before one of the pathological societies, but this was never reported in detail in any publication. Accordingly, I feel that this case of mine should also be recorded.

The patient was a woman, age 34, with a typical syndrome of hyperplastic hyper-

THE THYROTOXIC PATIENT

thyroidism. She was treated with thiouracil 0.6 Gm. daily, and the basal metabolic rate came to normal in about six weeks. She was then given iodine for about ten days and bilateral subtotal thyroidectomy was performed. When the tissue removed was studied, there was an area of carcinoma, about 3 mg. in size, located in the center of both removed lobes. This was not a nodular goiter and was strictly an hyperplastic type. One could easily assume that this patient had carcinoma in the center of both lobes of the thyroid before thiouracil was administered. Yet, one must think in terms of carcinogenic stimulant, since in the tissue removed from this patient there were no adenomata, the areas of carcinoma were located in the middle of each removed lobe, and the area involved was very small.

The patient has remained entirely well since operation, and we have never considered this situation to be one of primary carcinoma. Up to this time, we have not given her any postoperative roentgen ray therapy. In view of the fact that attention has been called to the carcinogenic properties of this group of drugs, I feel justified in relating to you the above-described case of carcinoma, but do not feel that one case would justify any definite implications against the drug administered.

DR. HAROLD L. FOSS, Danville, Pa.: All of us interested in the problem of hyperthyroidism and its treatment are grateful to the three essayists for what they have told us regarding their experiences in the use of these new and remarkable drugs.

In discussing thiouracil with my staff I recently remarked that, because of severe complications following the use of this substance, the government must soon remove it from the market, and, therefore, was interested in hearing Doctor Lahey make something of the same statement. While it is almost specific when properly used, and with the patient under observation, it is a dangerous drug and possesses unpredictable potencies. Our incidence of agranulocytopenia has been high, with about 30 per cent of cases showing leukopenia. We have refused to accept patients unless they came regularly to the laboratory every ten days for a blood count or arranged to have it performed by their own physicians, who were prepared to report promptly to us any change in the white cells. Such complications, of course, are a thing of the past now that we have propyl thiouracil. As Doctor Bartels stated, there may yet be some other antithyroid drugs synthesized that will eliminate the 2 per cent of complications characteristic of propyl thiouracil. I was glad to hear Doctor Lahey state that we are now safe in using propyl thiouracil routinely in all cases of hyperthyroidism and as a preoperative measure.

May I refer for a moment to a group of patients who are benefited by propyl thiouracil and thyroidectomy, and about whom but little has been written. I refer to those patients with "exophthalmic goiter" yet without goiter. These patients are not problems so much of therapy as of diagnosis. In a review of 3,000 consecutive patients operated upon by the speaker, we found that approximately 8 per cent with definite hyperthyroidism had no goiters, or had glands that, when resected, weighed less than the 30-40 Gm. usually considered as normal in weight and size for adults.

A recent group of 96 consecutive patients with advanced hyperthyroidism and without thyroid enlargement, was studied. All had glands, on resection, weighing less than that of the normal adult thyroid. The average weight was 23 Gm. The average age was 38; the average duration of symptoms was slightly over 12 months. Many had been treated as heart cases and for years. Many had been on digitalis interminably. All had the classical evidences of hyperthyroidism except for the presence of goiter.

(Slides were shown of a number of illustrative patients with advanced hyperthyroidism, with markedly elevated basal rates, exophthalmos, sinus tachycardia, etc., yet without goiters.) These patients constitute an important group of toxic thyroid cases, patients who may readily be cured following propyl thiouracil treatment and thyroidectomy, yet are frequently overlooked because of the absence of a goiter.

DR. HOWARD MAHORN, New Orleans, La.: It would be an obvious advantage if patients could be prepared in a short period of time and brought to the same stage of

safety as if they were prepared over a long period of time. In 44 patients operated upon on my service since preoperative thiouracil and iodine in combination were used, 15 had a basal metabolic rate of over 50; eight were over 75, and one had an initial basal metabolism of +100. All were prepared and operated upon in three weeks. No stage-operations were done, and there was no mortality. One was operated upon when she had a metabolic rate above +50. This means that after the use of thiouracil and iodine the criteria of operability is entirely different from that when iodine alone is used. A patient with a rate of +35 after treatment with thiouracil and iodine is probably in the same risk-stage as a patient with +20 prepared with iodine alone. It may be possible to prepare many of these patients quickly in a short period of time with safety and yet without the necessity of waiting for the basal metabolism to reach an absolute normal. I realize that this is a small group upon which to base this conclusion, but it brings up this possibility which may be worth consideration.

DR. WARREN H. COLE, Chicago, Ill.: When the antithyroid drugs were introduced, most of us, including surgeons, were interested in the question as to whether or not patients with hyperthyroidism would be removed from the practice of surgery. Although I am convinced that hyperthyroidism should be eliminated before thyroidectomy is performed, I am of the opinion that thyroidectomy will be indicated in the great majority of cases; thyroidectomy will be unnecessary in only a small portion of cases. In a small series of about 30 cases followed by us at Illinois Research Hospital, longer than eight months after cessation of six to eight months drug therapy, we noted that almost 50 per cent have shown no evidence of recurrence. Offhand, that appears favorable, but I suspect this impression is erroneous, because if we wait long enough many will come back with recurrences. In general, the recurrences occur in those who had great toxicity, and the good results in those with mild toxicity and small glands. In reality this was a picked group, insofar as it contained a large number of patients with mild toxicity.

In patients with nodular goiter I believe there is a distinct danger of development of carcinoma if the goiter is left in place year after year. A recent study we made at Illinois Research Hospital revealing a much higher incidence of carcinoma in nontoxic nodular goiter than in toxic nodular goiter, has led me to this fear.

In closing, I want to make a plea that we not consider the thyroid problem as being solved, and not forget all the things we have learned the hard way in the last two decades. Twenty-five years ago the operative mortality was as high as 4 to 6 per cent, but it is now less than 1 per cent. It dropped because we applied an improved knowledge of physiology to our treatment. I want to call attention particularly to the necessity of improved nutrition as a prerequisite in preoperative preparation. Hyperthyroid patients must show a gain in weight before operation can be considered. The patient who comes to the hospital in crisis cannot be relieved by antithyroid drugs. Until the day arrives when a drug is found which will neutralize the thyroid hormone, we will have to struggle along in these patients with crisis with the knowledge possessed before antithyroid drugs were introduced. Until such a drug is found that patient will remain a problem; for this reason alone, we must not discard all the knowledge it has taken us two decades to accumulate.

However, I do wish to congratulate Doctor Astwood, and his associates, for their epochal and most valuable contribution to the problem of hyperthyroidism.

DR. WILLARD BARTLETT, St. Louis, Mo. (closing): It has been 45 years since my first trip to Rochester, Minnesota, on which occasion the great Will Mayo made one remark I shall never forget, particularly apropos to this subject. He said: "Our trouble is not that we do not know enough about surgery; our trouble is that we do not use our knowledge." So my plea tonight is that those who are interested follow those six criteria of operability I threw on the screen, and if all are adopted and met satisfactorily, there will be practically no deaths in crisis.

THE THYROTOXIC PATIENT

DR. FRANK H. LAHEY, Boston, Mass. (closing): I would like to add one or two points which we have learned. We have learned that it is wise to omit propyl thiouracil for seven or eight days before operation. We have seen agranulocytosis occur seven days after the last dose was given, and it would be undesirable to have agranulocytosis at the time of operation, during the time of wound-healing or in the presence of possible wound infection. For that reason we have omitted it during the last week.

The reason Doctor Bartels was pushed into using iodine and propyl thiouracil together throughout the treatment was because of crises or thyrocardiac cases which still come to us, and he has seen such patients under thiouracil alone become worse. We, therefore, want something more prompt than the delayed action of thiouracil, and that is iodine.

These patients can do anything during their period of preparation for the operation. They take it at home. They are not incapacitated. Their white cell and differential counts are forwarded to us by their family doctor.

When we first began to prepare these patients for operation, we thought if we got their metabolic rates lowered that, while they were not normal, the patients were good surgical risks and we could operate upon them and so save them time. That we have not found to be true. The degree of thyroid reaction is something that cannot be predicted and we have had dangerous reactions in inadequately prepared cases so that only hemithyroidectomies could be undertaken safely. Everyone knows that an occasional patient who looks to be a good risk will have an unexpected reaction, and such an occasional patient will die. Therefore, we urge very strongly that propyl thiouracil be administered until the metabolic rate in these cases is completely normal. By this plan we can be sure that there will be no reaction and, with the complication rate as low as it is with propyl thiouracil, in our opinion there is no excuse to submit these patients to operation until all the toxicity has been completely abolished.

The following example of such a complicated case is one that I have repeatedly employed. This is one of our personal friends, a woman, age 77, with a metabolic rate of +48, a weight loss of 35 pounds, and the presence of auricular fibrillation, moderate decompensation and diabetes. Under propyl thiouracil the basal rate was restored to normal, auricular fibrillation was abolished, compensation restored, the diabetes put under easy control. She was then submitted to operation and, following subtotal thyroidectomy, never had a pulse rate above 80. Had this patient been operated upon before being made completely nontoxic, it could, I believe, have been a completely different story.

As to whether or not iodine involutes these glands perfectly, there can be no question. We could not have prepared 660 cases with thiouracil or propyl thiouracil and iodine and not have brought about satisfactory operating conditions. All of us who operate upon these patients at the clinic have now done so many thyroid operations that if some of them had bled excessively or the technical difficulties had been great, we would immediately have heard complaints about them, and there have been none. I can assure you that the preparation of these patients with Lugol's solution will so involute the thyroid gland that they will be as satisfactory to operate upon when prepared with propyl thiouracil and iodine as patients with hyperthyroidism were when they were prepared solely with Lugol's solution.

DR. RAWLEY M. PENICK, JR., New Orleans, La. (closing): I would like to comment on Doctor Lahey's statement about involution with iodine. I think iodine will bring about involution. On the other hand, I have operated upon some patients given iodine simultaneously with thiouracil, and the gland was vascular and friable. I think probably the reason for this is that the patients did not have it long enough. I think it is possible to get a very satisfactory gland with iodine.

AN EVALUATION OF PULMONARY EMBOLISM FOLLOWING INTRAVASCULAR VENOUS THROMBOSIS*

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THE MANY VARIATIONS in the management of thrombosis and embolism have prompted us to review our 20 years' experience with these conditions. We have compiled our statistics from the records of the Strong Memorial and Rochester Municipal hospitals. The protocols of the 1,752 surgical autopsies have been carefully analyzed. The autopsy figures are accurate, but we are sure that the clinical records are incomplete owing to the inadequate recording and filing during the war years. This will weight our statistics toward the fatal side. Undoubtedly, many minor pulmonary emboli have been overlooked, especially those with vein ligation and recovery. Our principal effort has been directed towards evaluating those factors which seem to predispose to pulmonary embolism, both fatal and nonfatal.

Age.—In studying age distribution it is apparent that fatal pulmonary embolus is most common in surgical patients over 50 years of age. The 6th, 7th and 8th decades are the most unfavorable for the surgeon. The medical patients present a slightly earlier grouping, the majority being 40-70 years. This is without doubt due to the heart disease of rheumatic origin in the medical deaths in this northern part of the country (Figs. 1, 2, Table I).

Sex.—There were no significant differences in sex distribution.

Time of Postoperative Embolus.—Approximately 80 per cent of postoperative pulmonary embolism occurs in the first two weeks (Fig. 3).

Heart.—A factor of prime importance which stands out clearly is the condition of the heart. If the cardiac action is impaired by heart disease there is danger of a slowing of the peripheral venous circulation. Weakness of the cardiac muscle, incomplete valve closure, irregularities in cardiac rhythm may lead to congestion in the lung bases and in the peripheral circulation. Increased hydrostatic pressure and venous stasis offer ideal situations for the development of intravascular clotting. Clots form at stasis or eddy points wherever there is compression of the vessel wall from without, especially in the elderly. Patients in coma often have embolism as they lie completely immobile for long periods. This has a bearing on the frequency of embolism in brain cases. It probably accounts for a number of fatalities in the urologic group where uremia is so prevalent. On the basis of autopsy figures the

* Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 10, 1946.

PULMONARY EMBOLISM

evidence shows that the heart weight is materially higher in the patient with fatal pulmonary embolism. Taking 400 Gm. as the upper limit of the normal heart, the incidence of cardiac hypertrophy is much higher among patients with pulmonary embolism than in the group in whom no emboli were found. When one considers anatomic evidence of cardiac decompensation as found at postmortem the differences are even more striking (Table II). The influence

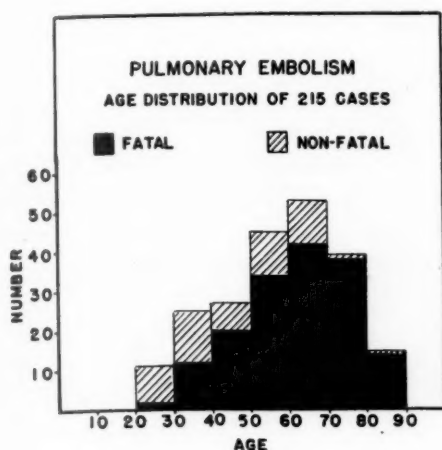


FIG. 1

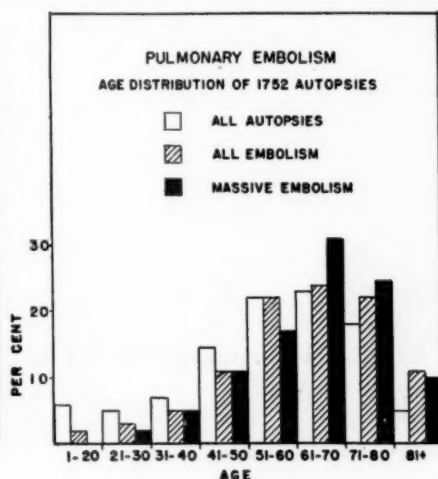


FIG. 2

FIG. 1.—Age distribution of 215 cases of pulmonary embolism found in 1,752 autopsies.

FIG. 2.—Age distribution of 1,752 autopsies in relation to age distribution of all pulmonary emboli and massive (fatal) pulmonary emboli found at necropsy.

TABLE I

FATAL PULMONARY EMBOLISM IN MEDICAL AND SURGICAL PATIENTS

Age Distribution		
Years	Medicine Number	Surgery Number
10-19.....	4	0
20-29.....	3	2
30-39.....	12	12
40-49.....	27	20
50-59.....	31	34
60-69.....	60	42
70-79.....	36	38
80+.....	5	14
Total.....	178	162

Includes patients who had neither operations nor clinical evidence of thrombophlebitis.

of heart disease is even more strikingly evident in the clinical study of pulmonary embolism. Forty-one per cent of the patients who survived after one or more pulmonary emboli had no heart disease. Only 8 per cent who had any evidence of heart disease survived. No patient survived a pulmonary embolus who had cardiac decompensation (Table III).

Mobilization.—It has always been the policy in our hospitals to mobilize patients early. Older patients have been made ambulatory within 24 hours of operation whenever possible. We have been able to do this because our wounds usually have been sutured with silk and, thus, can withstand early strains. We did this as far back as 1928 with the idea of avoiding hypostatic pneumonia. One of our conclusions at that time was: "Mobilization of the aged patient without undue concern about the incision seems to be a factor of safety in preventing postoperative complications."⁶ We consider it just as important

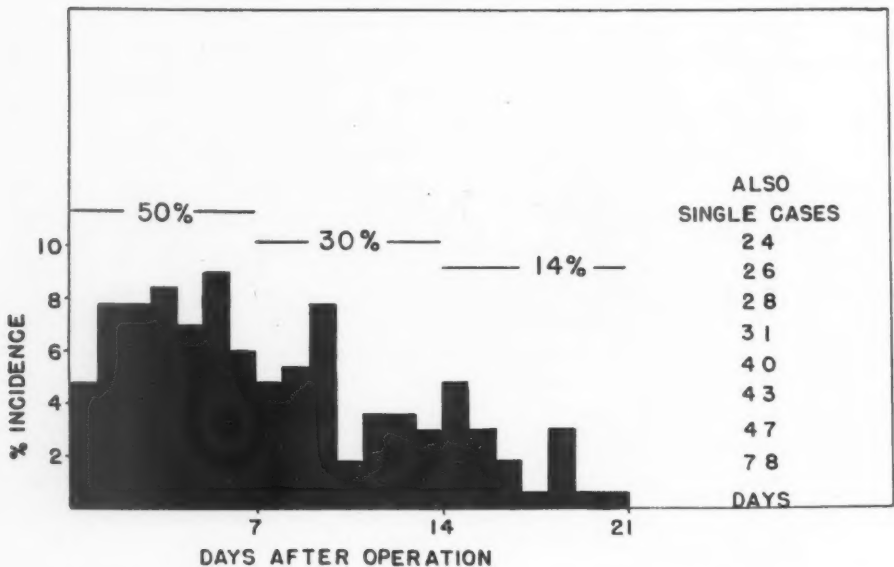


FIG. 3.—Day of occurrence of postoperative pulmonary embolism in 168 cases.

to mobilize the patient in bed by means of exercises, frequent turning, hyper-ventilation and by encouraging him to change his position. This is not possible in a heavily sedated patient. We prefer to have our patients on the uncomfortable rather than the too comfortable side. Early ambulation often means a short period of standing with assistance or sitting in a chair. While this is important it only occupies a small fraction of the day. The patient's own muscular exertion is the variable that is important.

Position.—Position in bed may be a factor of importance in contributing to peripheral venous stasis. The common practice of propping up the knees by the mechanical breaking of the bed and the similar elevation of the head and trunk,—the so-called "jack-knife position,"—would appear to favor puddling at the ankles and femoral—inguinal creases, with subsequent impairment of venous return. The popliteal and femoral inguinal creases would contribute definite points of pressure on the vascular channels. All together if the

PULMONARY EMBOLISM

position be maintained for a few hours it constitutes a definite hazard. In contrast to this, if the lower limbs were elevated by raising the foot of the bed so that the limbs were about 15° above the horizontal, drainage from the vessels would be promoted, there would be an increase in the volume blood flow into the caval circulation, and stasis would be prevented. The head could be raised to a comfortable level at the other end of the bed,—a matter of 15°–20° usually (Fig. 4).

TABLE II
CARDIAC STATUS IN RELATION TO PULMONARY EMBOLISM
1752 Autopsies

	No Emboli	Small Emboli	Large Emboli
Trauma:			
Number of observations.....	235	32	14
Mean weight hearts.....	355	370	425
Hypertrophied hearts.....	25%	31%	57%
Failure.....	8%	28%	28%
Appendicitis:			
Number of observations.....	40	5	2
Mean weight hearts.....	340	365	445
Hypertrophied hearts.....	28%	25%	2
Failure.....	15%	20%	0
Peptic Ulcer:			
Number of observations.....	69	13	2
Mean weight hearts.....	360	330	405
Hypertrophied hearts.....	22%	23%	50%
Failure.....	17%	39%	50%
Intestinal Obstruction.			
Number of observations.....	66	10	2
Mean weight hearts.....	365	350	375
Hypertrophied hearts.....	27%	20%	50%
Failure.....	20%	40%	100%
Benign Prostatic Hypertrophy:			
Number of observations.....	74	23	19
Mean weight of hearts.....	425	450	435
Hypertrophied hearts.....	47%	57%	74%
Failure.....	24%	22%	53%
Gangrene:			
Number of observations.....	46	13	7
Mean weight hearts.....	380	400	420
Hypertrophied hearts.....	39%	43%	43%
Failure.....	13%	61%	71%
All Autopsies:			
Number of observations.....	1432	199	121
Mean weight hearts.....	325	360	390
Hypertrophied hearts.....	21%	28%	39%
Failure.....	16%	27%	28%

Position on the operating table may also be criticized especially in urologic, gynecologic and rectal operations. Here, the tendency to put patients in stirrups with flexed knees and hips for fairly long periods may well be instrumental in starting the intravascular clots which manifest themselves as emboli later. It is our custom following operation where this position has been used to completely extend the legs at the knees and to elevate the whole limb to the vertical at the same time gently stroking over the veins to empty them.

Other Factors.—There are many other factors which probably influence intravascular clotting, such as paralytic ileus, obesity, dehydration and varicose

veins. We have attempted to evaluate these in our clinical studies of pulmonary embolism and their incidence is tabulated. (Table IV) An incidence of 38 per cent of paralytic ileus in the fatal emboli may well be significant but we have no comparable standards for reference. We were surprised to find that only 10-12 per cent of our patients with pulmonary embolism had varicose veins.

We have found that infection is present in 75 per cent of our cases with embolism, whether fatal or nonfatal. By infection we refer to any type of

TABLE III
INFLUENCE OF HEART DISEASE ON PULMONARY EMBOLISM

	Nonfatal	Fatal
No heart disease.....	41%	59% (100 cases)
All heart disease.....	8%	92% (98 cases)
Cardiac decompensation.....	0	100% (57 cases)

TABLE IV
FACTORS INFLUENCING PULMONARY EMBOLISM
112 Cases, 29 Living, 83 Fatal

	Nonfatal		Fatal	
	Present %	Absent %	Present %	Absent %
Infection.....	72	28	76	24
Paralytic ileus.....	31	69	38.5	61.5
Obesity.....	17	83	28	72
Dehydration.....	3.5	96.5	18	82
Varicose veins.....	10.5	89.5	12	88

bacterial invasion of the body, such as pneumonia, genito-urinary tract infection, peritonitis, septicemia, cellulitis, wound infection, gangrene of extremities, empyema, etc. It is by no means necessary that infection be in the immediate neighborhood. Infection is known to cause increased coagulability of the blood, and because of this is probably a potent factor in thrombosis.

Lesions which Predispose to Pulmonary Embolism (exclusive of gynecologic conditions).—The common lesions encountered in autopsies on surgical patients are presented in Table V. The gross incidence of pulmonary embolism is 17 per cent, while 6.5 per cent of all patients had large emboli which occluded one or more major branches of the pulmonary artery. All emboli that possibly might have originated in the right heart have been eliminated from this series. The patients with benign prostatic hypertrophy, uncomplicated herniae, gangrene of the extremities and carcinomas of the colon and rectum have by far the highest incidence of fatal pulmonary embolism. Patients suffering from severe traumatic injuries have an average number of embolic episodes, but it is probably significant that almost all of the fatal pulmonary emboli were found in old ladies with fractured hips. It is interesting

PULMONARY EMBOLISM

that no fatal pulmonary emboli were found among those patients who died from complications of ulcerative colitis and esophageal carcinomas. Brain tumors deserve especial mention since the incidence of fatal pulmonary embolism exceeded that of the entire series. Probably none of these were suspected clinically.

A summary of our clinical experience with pulmonary embolism is recorded in Table VI. The ratio of fatal to nonfatal embolism is highest in operations on the brain and genito-urinary system. It is interesting to note that the same proportion of patients survived pulmonary embolism after gynecologic surgery as they did after abdominal surgery.

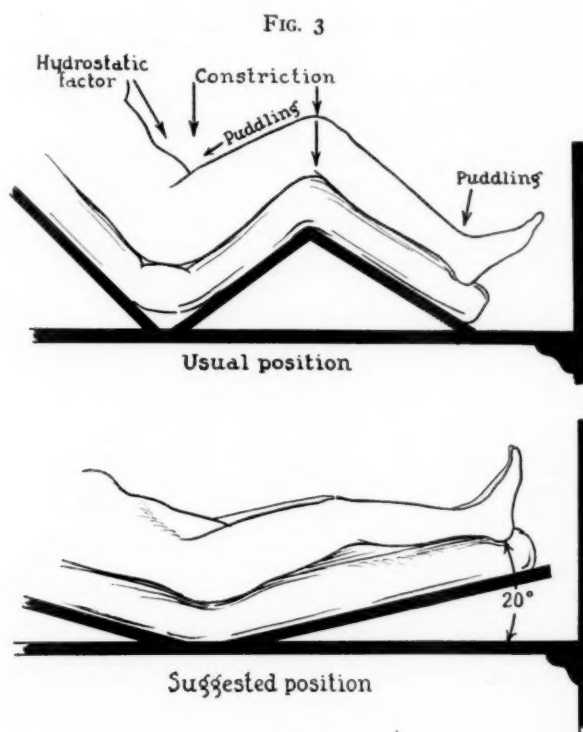


FIG. 4

FIGS. 3 and 4.—Demonstrating the usual and the recommended methods of adjusting the bed.

None of our patients are known to have survived pulmonary embolism after a brain operation, major amputation, or abdominoperineal resection of the rectum. There have been five instances of pulmonary embolism following ligation for varicose veins. There has been one fatality following such an operation. There has been one fatality by pulmonary embolism following bilateral therapeutic ligation for phlebothrombosis and at least one where non-fatal emboli have occurred following ligation.

Sources of Emboli.—The Swiss and German investigators^{3, 5} have given rather conclusive evidence that the majority of the thrombi from which emboli occur are to be found in the legs. As early as 1934, Homans⁴ pointed out the importance of these observations, and suggested prophylactic and therapeutic vein ligation in pulmonary embolism. At the present time there seems to be rather general agreement in this country among both surgeons and pathologists that the legs furnish the main source for the emboli. The postmortem examination as done in America really contributes very little to the knowledge of the source because of restrictions against dissecting the extremities. It is

TABLE V
PULMONARY EMBOLISM IN RELATION TO COMMON SURGICAL LESIONS
1752 Autopsies

Lesion	No Embolism		All Embolism			Massive Embolism			
	No.	Mean Age	No.	Incidence	Mean Age	No.	Incidence	Mean Age	Massive/All
Appendicitis.....	55	42	10	15%	60	4	6%	55	40%
Peptic ulcer.....	65	60	16	20%	57	2	2.5%	79	13%
Intestinal obstruction.....	77	59	13	14.5%	64	2	2%	69	15%
Infection.....	250	50	45	15%	55	7	2.4%	59	16%
Colitis.....	18	47	7	28%	52	0	0	0	0
Pancreatitis.....	18	58	5	22%	66	1	4%	75	20%
Trauma.....	229	52	47	17%	70	16	6%	74	34%
Gangrene.....	49	63	22	31%	70	7	10%	62	32%
Gallstones.....	76	61	13	15%	59	6	7%	55	46%
Hernia.....	15	58	5	25%	67	3	15%	67	60%
Benign prostatic hypertrophy	81	71	42	34%	74	20	16%	73	48%
Other genito-urinary.....	47	56	11	19%	58	5	8.6%	56	45%
Carcinoma stomach.....	62	61	16	20.5%	59	5	6%	53	31%
Carcinoma colon and rectum	108	62	26	19%	63	13	10%	68	50%
Carcinoma bladder.....	38	65	6	14%	63	2	5%	57	33%
Carcinoma prostate.....	69	69	16	18.5%	75	7	8%	74	44%
Carcinoma pancreas and biliary system.....	50	60	7	12%	57	4	7%	59	57%
Brain tumors.....	96	43	17	14%	49	9	8%	49	53%
Carcinoma esophagus.....	26	60	2	6%	71	0	0	0	0
Other neoplasms.....	143	55	26	15%	61	3	2%	57	12%
Other diseases.....	63	50	9	12.5%	60	6	8%	55	67%

apparent that fatal emboli come from the larger veins, and previous small warning emboli are probably an early stage of the thrombotic process in smaller veins.

Neither our clinical nor our autopsy experience contributes a great deal to the knowledge of the source of pulmonary emboli, but indirect evidence makes us agree with the present-day theory. We now feel that it is unlikely that fatal pulmonary emboli have their origin from smaller thrombosed veins about an operative site. When embolism occurs from such a site, it usually consists of multiple small septic thrombi. When there is no evidence that the legs or the pelvic veins are involved, the heart is probably the source. We have been amazed that patients receiving continuous intravenous therapy, who have many superficial veins of both arms and legs thrombosed, rarely have

PULMONARY EMBOLISM

pulmonary emboli. The only incidence of pulmonary embolism which we could attribute to intravenous therapy resulted after using varicose veins of the leg as the only available situation for intravenous therapy. This occurred in a patient with extensive burns of the trunk and upper extremities. The introduction of blood was followed by two nonfatal emboli and a subsequent phlebitis.

Case No. 216681.—A 46-year-old electrician was readmitted to Strong Memorial Hospital a few minutes after receiving electrical flash burns of the face and hands. His clothing had caught fire and burned his arms, neck and trunk. At the time of admission shock had not yet become clinically evident. Examination revealed second-degree burns of the face and hands and extensive third-degree burns of the trunk and arms. The burns were treated with compression dressings, and plasma was given intravenously. After the first day, he received daily whole blood transfusions and intravenous Amigen. Because no arm veins were available leg veins were used for intravenous injection and at times

TABLE VI
PULMONARY EMBOLISM
Type of Operation

	Living	Fatal	Dead of Other Causes
Neurosurgery (brain)	0	6	2
Genito-urinary	6	32	0
Bone and joint	3	11	2
Abdominal	15	31	7
Abdominoperineal resection rectum	0	4	4
Thyroid	1	2	0
Drainage abscess	1	7	1
Amputation	0	9	0
Ligation of veins	6	1	0
Gynecologic	8	18	0
Total	40	121	12

it was necessary to use varices of the legs. Thrombophlebitis developed in the right leg on the 10th hospital day. On the following day he developed signs of a left pulmonary infarct. Three days later there was an episode of pain in the right chest. Because of the very extensive phlebitis, vein ligation was not considered feasible, so anticoagulant therapy with heparin and dicumarol was started. No further emboli occurred and skin grafting of the third-degree areas was accomplished without difficulty. The phlebitis had subsided at the time of discharge.

THE PROBLEM

Our present method of therapy has been based on the following impressions which we have gained from our own past experience, and that of others: (a) We consider clinical thrombophlebitis a dangerous situation, and it is a warning which should not be ignored, as there is a 25 per cent chance of pulmonary embolism.¹ In thrombophlebitis there is a 6 per cent chance of a fatal outcome.¹ Recently, there has been a tendency to feel that once phlebitis has become established there is very little danger of a thrombus breaking loose in the blood stream as an embolism. In our experience, we have

seen patients who have had repeated pulmonary emboli, some of them fatal, at a time when phlebitis was definitely present. We realize that the embolus may have arisen from the normal leg rather than from the involved one. Consequently, in dealing with this problem we believe that a bilateral ligation should be done. We formerly used diodrast to help us in deciding what to do, but this has been abandoned because we were unable to interpret venograms correctly, and the diodrast is perhaps irritating to the veins. (b) When there has been a pulmonary embolism, even though there may be no gross clinical involvement of the legs, this warning *must* not be ignored. There is a 44 per cent chance of a subsequent embolus, and an 18 per cent chance of a fatal one.¹ In some instances there may be minimal clinical signs which will lead one to suspect the involved extremity, but in others repeated examinations by experienced individuals have failed to elicit pain, tenderness, or a positive Homans' sign. Under these circumstances we now believe that bilateral femoral exploration and ligation should be performed.

Case No. 154980.—A 61-year-old woman was admitted to the Strong Memorial Hospital on February 9, 1944. She had a breast carcinoma for which a radical mastectomy was done on February 15, 1944. She was out of bed sitting in a chair on the 4th postoperative day. Her wound healed without infection. The stitches were removed on the 7th postoperative day. On the next day, at 1:00 P.M., she had an acute episode which was diagnosed as either a pulmonary embolus or a coronary occlusion. Signs of pulmonary infarction became definite at the right base. Repeated examinations of her legs gave no indication of phlebitis. She was kept in bed, and improvement was progressive until March 9, 1944, when she had a second episode, and an increased area of involvement in the right lung. She still showed no evidence of phlebitis. On the 33rd postoperative day, she had pain in her left leg for the first time. Under local anesthesia, both femoral veins were ligated above the clots which were present in each. One hour after operation she complained of severe pain in the left chest, became cyanotic, went into shock, and died shortly thereafter. Postmortem examination showed pulmonary emboli with pulmonary infarction. There were thrombi in the right iliac veins. Microscopic sections showed these to be antemortem clots.

We are not yet convinced as to the proper treatment for the patient who complains of minimal tenderness in the calf, and who has not had a pulmonary embolus. Perhaps this would be the type of patient who would be benefited by heparin and dicumarol. Our experience with these drugs has not been sufficient to answer this question. Barker's¹ report, however, would seem to support this therapy.

The rationale for the ligation of the major veins of the extremities or the vena cava in patients who have presented neither thrombosis nor embolic phenomena must next be considered. This procedure is based on the presumption that a certain percentage of such individuals will ultimately have thrombosis and embolism. The therapy is regarded as a prophylaxis against such a complication. As there is no way of determining which side may be the offender, bilateral femoral ligation must be done. It is logical to make it a single higher ligation, namely, the vena cava, as it also covers the possibility of thrombosis arising in the large pelvic veins. It also gives a chance for

better collateral circulation as the ligation is higher. As far as we can determine no one has considered ligation in continuity, with the chance of later recanalization. It is probably not done because of fear of overlooking loosely attached clots above the ligature. Objections to tying the normal vena cava are that it calls for a major-type operation, that swelling and discomfort of the legs are produced for an indefinite period, and that the pain of this distention may require sympathetic blocks or sedation. Some writers claim that pain and inflammatory reaction are relieved by the temporary interruption of the sympathetics running along the vein walls. This has not been the experience of most surgeons. No one has emphasized the fact that after division of a major vessel, with ligation, thrombosis is the natural healing process, the thrombus propagating itself up to nearest branch. This being so, the surgeon can have no comfort that his therapy will prove effective. The problem is simply transferred to a higher level if the underlying causes for the condition have not been corrected. We have not tied the veins on patients who do not show either thrombosis or embolism because we believe that it is too radical surgery. Too many veins would be tied unnecessarily to ward off danger in too few patients.

Surgical intervention in suspected cases of phlebothrombosis is bound to damage the venous return from the legs in a large proportion of cases. Probably the majority of these suspects do not actually require surgical intervention but, as of today, it seems impossible to evaluate the potentialities of a given case. In other words, surgical therapy for phlebothrombosis is unsatisfactory but is being forced on the attending surgeon.

The problem of phlebothrombosis can only be solved by further investigation of the physicochemical aberrations of the venous circulation in the patient who is put to bed. We need more information regarding the mechanism of venous return from the legs; on the maintenance of venous pressure; on the blood clotting mechanism; and on the viscosity and the wetting power of the blood. Pulmonary embolism is by no means an exclusively surgical problem. The best position to take on any adult patient who must be confined to bed is that he may be a potential candidate for thrombosis and embolism. Measures should be promptly put into effect to minimize these possibilities. These measures are active mobilization by means of stated exercises at stated periods; maintenance of cardiac efficiency if possible; hydration; minimal sedation and elevation of the legs above the cardiac level. Successful prevention depends on active coöperation of all medical attendants as well as of the patients themselves.

REFERENCES

- ¹ Barker, N. W., Cromer, H. E., Hurn, M., and Waugh, J. M.: The Use of Dicumarol in the Prevention of Postoperative Thrombosis and Embolism: With Special Reference to Dosage and Safe Administration. *Surgery*, 17, 207, 1945.
- ² Dennis, C.: Disaster Following Femoral Vein Ligation for Thrombophlebitis, *etc.* *Surgery*, 17, 264, 1935.
- ³ Dock, W.: Use and Abuse of Bed Rest. *N. Y. State J. M.*, 44, 724, 1944.

- ⁴ Homans, J.: Thrombosis of the Deep Veins of the Lower Leg Causing Pulmonary Embolism. *New England J. Med.*, **211**, 993, 1934.
- ⁵ Hunter, W. C., Krygier, J. J., Kennedy, J. C., and Sneed, V. D.: Etiology and Prevention of Thrombosis of the Deep Leg Veins. *Surgery*, **17**, 178, 1945.
- ⁶ Morton, J. J.: Surgical Care of Patients in the Extremes of Life. *Am. Jour. Surg.*, n.s., **30**, 92, 1935.

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DISCUSSION.—DR. ARTHUR W. ALLEN, Boston, Mass.: I would like to congratulate Doctor Morton on this survey of his experience because it is basic and because it coincides almost identically with our own experience at Massachusetts General Hospital, in an analysis of this problem made several years ago. I cannot give an account of all our studies in this discussion, but I want to emphasize that the management of the problem as a whole should be definitely divided into two categories. One is that of prophylaxis; in suitable cases that may be anticoagulant therapy. This is very effective but it must be carried out under strict laboratory control. The other method of prevention is to admit that, in patients with certain lesions, beyond a certain age, the chance of embolus is very great, and that prophylactic interruption of the deep veins of the leg is a logical procedure. The other chief consideration is that of treatment after thrombosis or infarct has occurred.

Up to October 1st of this year we have treated by bilateral femoral vein interruption 1,060 patients, after infarct or after definite leg signs have been noted. In five of these patients who had had sublethal emboli before femoral vein interruption, subsequent emboli produced death. In addition, in the older age-group, we have interrupted the veins prophylactically in 458 cases. There have been five instances of mild phlebitis and one fatal embolus in this series. In 458 patients, as nearly similar as we could determine as to age, sex, trauma, type of operation, illness, *etc.*, without prophylactic femoral vein interruption, there were 55 instances of phlebitis and 26 fatal emboli. This I think is significant.

I wish to stress, at this time, that in none of these more than 1,500 patients subjected to bilateral femoral vein interruption in our hospital has there been any loss of life or loss of limb as a result of the operation. Furthermore, I wish to say that we have found that interrupting the normal vein caused practically no sequelae of any importance. This interested us a great deal; they did not develop thrombophlebitis and swelling afterward, as we feared they might. We feel that this prophylactic attack in the vulnerable age group is justified.

There were 110 cases in each group with fracture in or about the hip. In the 110 cases that had prophylactic interruption there were two instances of mild phlebitis and no fatal embolus. In the immediately preceding 110 cases there were 20 instances of phlebitis and 11 fatal emboli. It has been known for a long time that cases with injuries to the leg are particularly prone to develop thrombosis and embolism. In 49 leg amputations where prophylactic interruption was done, there were no instances of phlebitis and no emboli; whereas in the control group of 49 there was one phlebitis that was recognized and six deaths from pulmonary embolism. In gastrectomy in this age-group, in 48 cases there were nine instances of phlebitis in cases not interrupted and three fatal emboli. In 20 cases of hernioplasty that had prophylactic interruptions, one fatal embolus occurred. We think there might have been an error in technic in the interruption of the veins in this case. In 20 cases of the same type there were three instances of phlebitis and one fatal embolus.

There were 20 cases of decompensated heart disease in each group. Our medical men are quite different, apparently, from those in Rochester. We are sometimes embar-

PULMONARY EMBOLISM

rassed by their insistence on having this procedure done; they frequently say please do it, rather than asking our opinion about its necessity.

We believe that prophylactic dicumoral is suitable for patients under 60 years of age who had no contraindications to its use. We think that prophylactic femoral vein interruption is logical and safe for patients beyond the age of 60.

Treatment may be of three types: femoral vein interruption, anticoagulents and lumbar sympathetic procaine blocks. These may be used alone or in conjunction, depending upon the indications.

DR. FREDERIC W. BANCROFT, New York, N. Y.: Early mobilization, in the hands of most of us, has not been as successful as it might have been. All have seen cases of phlebothrombosis and embolism develop in patients mobilized early. To some of us this meant having the patient out of bed and sitting in a chair. If you will visualize the picture that Doctor Morton showed, with the patient in the Gatch position, you will recognize how much worse it is to have a patient sitting in a chair, feet down, and the patient quiescent. There is a pressure on the popliteal space and acute flexion at Poupert's ligament associated with venostasis. Actually, early mobilization should be that a patient gets out of bed and walks. When tired, he should return to bed, with the bed nearly flat. While in bed, he should constantly utilize his legs in active motion, as described years ago by Doctor Pool.

There is another type of phlebothrombosis which originates in the pelvic veins and not in the superficial and deep veins of the leg, as described by Doctor Allen. In order to emphasize my points I should like to mention briefly two cases:

Case 1.—A woman who had had a cesarean section followed by a normal convalescence. She went home on the 10th day postoperative. Four days after her return home, she had sudden pain in her chest, with an elevation of temperature. She was readmitted to the hospital. On radiologic examination, it was difficult to determine whether her symptoms were due to virus pneumonia or an embolism. There was no pain nor swelling in either thigh or leg. Nine days later, this patient developed evidence of deep thrombosis on the left side. I was called in to see her and operated, and sucked out a thrombus from the iliac vein. The suction apparatus did not work well and I was not satisfied that I had removed the entire thrombus. Following this procedure the patient was better, but on the 9th day following she had a sudden attack of pain in the right chest and again evidence of an infarct by radiologic examination. I did a thrombectomy on this side. The patient, however, succumbed from the involvement of the chest. On postmortem examination, there was found a thrombus from the left side protruding about two inches upward into the vena cava; there were massive emboli in both lungs. Microscopic examination of the uterus showed that the pelvic veins were the cause of the original phlebothrombosis. They had extended into the iliac vein and were not noted in the thigh until the retrograde thrombosis had extended downward.

COMMENT.—It might have been better in this case, if the patient had not been so desperately ill, to have ligated the vena cava.

Case 2.—This patient was a young woman who had had a normal pregnancy. Eight days following delivery she had pain in the left chest and radiologic evidence of a probable infarct. Both thighs and legs were normal on examination. With the memory of the previous case in mind, we operated simultaneously on the femoral veins under local anesthesia just under Poupert's ligaments. On opening the veins, no clots were detected but each vein was in definite spasm. A sucker was passed up for a distance of about eight inches in each vein, and thrombi were removed by suction until free bleeding returned. With the exception of the fact that the patient needed immediate transfusion due to blood loss, her convalescence was uneventful and she returned home on the 9th postoperative day.

COMMENT.—Obviously in this case the thrombus had started in the pelvic veins.

I still believe that the study made by Dr. Stanley-Brown and me some years ago indicates that there are potential intravascular clotters as well as potential bleeders. At that time we made a routine examination of the prothrombin and fibrinogen of all anteparturient and postoperative cases. We felt that everywhere in the body are *hyper* and

hypo conditions, such as hyperthyroidism, and hypothyroidism, hyperacidity and hypoacidity. Therefore, if there are potential bleeders, there must be potential clotters. In our analysis of about 1,600 cases we found that about 14 per cent were potential clotters. All our accidents occurred in this 14 per cent, but these accidents constituted only 2 per cent of the 14 per cent. On analyzing the remainder of the 14 per cent, we found that they had a rather prolonged convalescence, in that the temperature remained slightly elevated and there was evidence of some malaise, and we assumed that some of these might have been deep thromboses which we did not recognize.

It would be a great help to us all if we knew pre-operatively which cases were likely to develop a postoperative accident. While I recognize that the prothrombin test is not as accurate as it might be, I still believe that it may be an indication of the potential patient who may develop phlebothrombosis.

DR. WALTER D. WISE, Baltimore, Maryland: I want to say a word about prophylaxis, not from an operative standpoint but from the anticoagulant viewpoint. I want to make a preliminary report of an intensive study of the use of dicoumarol in my hospital which has been going on for some years as a therapeutic measure, and more recently as a prophylactic. There will be a paper published which includes only surgical patients, not including the medical cases that have been spoken of. The results lately, since we have been using dicoumarol prophylactically, are so good that we hesitate to bring them out because I know that no such record as this can be maintained. It is possible that the good results are not due to dicoumarol alone, but to a combination of procedures such as has been outlined.

In Mercy Hospital in Baltimore, 4,000 to 4,500 operations are performed in a year, including deliveries but excluding nose and throat cases. In the four-year period from 1939 to 1942, inclusive, there were 50 cases of postpartum and postoperative thrombophlebitis, 22 cases of pulmonary infarction and eight deaths. In 1943 the use of dicoumarol was begun. From 1942 to 1946 there were 41 cases of thrombophlebitis with 13 pulmonary emboli and four deaths. In 1944 a rather intensive program of prophylactic use of dicoumarol was started. The staff has cooperated very well and it has become almost routine. The chief of the laboratory is willing to work long hours, and does, and is very much interested in it, and the results are that in 1945 only six cases were diagnosed as thrombophlebitis, and so far in 1946 there have been six. In 1945 there was one pulmonary embolus, two so far in 1946, and no deaths in those two years. That record can hardly be maintained. It may be coincidental, to some degree, but it does give, in a medium-sized service, some reason to pay a little more attention to anticoagulant prophylaxis and therapy than is being done, according to what we have heard today.

DR. ROY D. McCURE, Detroit, Mich.: Recently we had a symposium on this subject at the Sectional Meeting of the American College of Surgeons in Detroit. One of the speakers was Dr. Gunnar Bauer, of Sweden. He presented the results of heparin therapy in two Swedish hospitals, and the statistics indicated that the drug was of value in the prevention of fatal pulmonary embolism. He stated that he preferred heparinization rather than femoral vein ligation. There is great interest in heparin among the Swedish doctors. Dr. Eric Jorpes, of Stockholm, who is in this country at the present time, has just published a revised and enlarged edition of his monograph on heparin.

At the Henry Ford Hospital, we have used the anticoagulants and vein ligation. Dr. Conrad Lam and Dr. Donald Hooker have recently published the statistics on our cases (*ANNALS OF SURGERY*, 123, 221, 1946). They found that since the adoption of anticoagulant therapy and prophylactic femoral vein ligation, there has been a very low mortality rate in cases selected for treatment. However, these measures did not prevent a number of sudden and unexpected embolisms. They thought that early ambulation offered the most promise as a preventive measure easily applicable to most surgical patients.

PULMONARY EMBOLISM

DR. ROLLIN A. DANIEL, JR., Nashville, Tenn.: Dr. Richard Crutcher and I are completing a study of this problem at the Vanderbilt University Hospital, based on clinical and autopsy records over a 15-year period, 1930 to 1945. During this time there were 83,984 admissions to the hospital; 30,000 operations were performed; 2,749 autopsies were performed, representing 63 per cent of the patients who died in the hospital during that time.

Among the autopsy cases there were 55 in which pulmonary embolus was probably the cause of death. Nineteen of these patients had more than one embolus. Thirty-six patients had a single massive embolus.

The 55 autopsy cases were divided into two groups as follows:

1. Those patients who could not have recovered from their disease had pulmonary embolism not occurred. There were 21 patients in this group. Ten of these had cardiac failure which could not be controlled by adequate digitalization and all other supportive measures; seven had far-advanced malignant disease; one had severe tetanus, two widespread abdominal and pelvic infections, with septicemia, and one had bilateral congenital cystic kidney with pyelonephritis and uremia. All these patients were in the terminal stages of their disease.

2. Those patients who probably would have recovered had pulmonary embolism not occurred. There were 34 patients in this group. Analysis of this group revealed that six patients had massive edema involving the extremities, caused by hypoproteinemia or nephritis. Clinical evidence of intravascular clotting would have been extremely difficult to detect in these patients. There were, therefore, only 28 patients in whom phlebothrombosis might have been noted and in whom one might have been willing to perform operative procedures designed to prevent pulmonary embolism.

We feel that it is important to emphasize the fact that more than a third of the fatal emboli occurred in patients with incurable diseases.

DR. JOHN J. MORTON, Rochester, N. Y.: I wish to thank all the discussants for the kind way they have handled me. What I meant to emphasize is that this is not an exclusively surgical problem by any means. It is a problem of putting patients to bed. If your patient is an adult, he will get thrombosis if you keep him there and do not take measures to prevent it. Early ambulation is a good thing. In most cases this may mean a few steps and then back to bed. We wish to stress that the exercises in bed are more important. These keep the muscles in tone and the veins drained.

We may come to tying normal veins, but we have not done it yet, and I want to see a few more indications before we do.

THE STUDY OF MALIGNANT CELLS WITH PHASE DIFFERENCE MICROSCOPY*

W. M. FIROR, M.D., AND G. O. GEY, M.D.

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MODERN SURGERY has made significant contributions to the welfare of patients afflicted with malignant disease, but modern surgery has made no significant contribution to our understanding of malignant processes. The efforts of pathologists in this field have been similarly futile. For more than thirty years living cells have been observed and recorded photographically, without giving any insight into those essential physiologic alterations that constitute malignancy. For many years biochemists have tried to detect some significant variation between normal and malignant tissue. Their efforts to find some qualitative abnormality commensurate with the abnormal behavior of malignant tissue have failed. Quantitative differences between benign and malignant tissue have, however, been described, and during the past three years exceedingly significant changes have been noted in the field of enzymology. Biochemists for more than 15 years have given us a series of carcinogenic components, but the action of these substances upon intracellular constituents is not fully understood. Efforts to correlate chemical alterations with cellular structure are just beginning to bear fruit. Midway between the realm in which the chemist works and that of the microscopist lies a zone which, heretofore, has not been open to scrutiny. I refer to those intracellular components which are larger than molecules and yet too small to be seen by the ordinary light microscope. During the past three years two technics have been started which permit observation and study of these intracellular constituents.

The first of these new methods is electron microscopy. The work of Porter, Claude,¹ and others, has already enlarged our knowledge of intracellular structure, and in the next few years one can reasonably expect many important additions to this knowledge. The second technic is phase difference microscopy, and it is this technic which we shall briefly describe and illustrate this morning. Suffice it to say, the essential feature of this method consists of altering the contrast in the image by introducing in the microscope a diffraction plate which changes absorption and optical path differences. The advantages of phase difference microscopy are great when one deals with homogeneous material, such as cytoplasm. This presentation is not a verbal description, but a visual demonstration of what can be accomplished by this method. I would like to point out that in the early part of the film I am about to show,

* The authors wish to thank the American Optical Company for furnishing them with phase contrast equipment.

Read before the 58th Annual Session of the Southern Surgical Association, Hot Springs, Va., December 11, 1946.

PHASE DIFFERENCE MICROSCOPY

one can see the movement and behavior of the cell membrane. Heretofore, this has not been clearly seen with the ordinary light microscope.

It is suggested that you focus your attention on the following features of this plasma membrane that surrounds every cell within the body. It is flexible, it is contractile, it is tenacious, and it is porous. The amazing fact is that, when a cell divides, the cell membrane remains intact. The second feature to which I direct attention are certain components of the cell which, heretofore, have not been visualized in living tissue, particularly the network in the central cell mass and the Golgi apparatus. Finally, in the last portion of the film one can see the behavior of certain cell constituents. In particular, I refer to the movement of the mitochondria which shuffle back-and-forth from the edge of the cell to the central cell mass. This is particularly significant when one remembers that recently it has been shown that the mitochondria contain nearly all of certain respiratory enzymes.³

(Motion Picture)

This presentation is in no way exhaustive. It has served merely to give us a glimpse into the possibilities of a new technical procedure and to show the way we are thinking, and possibly give a suggestion as to the direction in which we are heading.

REFERENCES

- ¹ Porter, K. R., Claude, A., and Fullam, E. F.: *J. Exp. Med.*, **81**, 233, 1945.
 - ² Bennett, A. H., Jupnik, H., Osterberg, H., and Richards, O. W.: *Trans. Am. Mic. Soc.*, **65**, No. 2, April, 1946.
 - ³ Hogeboom, G. H.: *J. Biol. Chem.*, **162**, 739, 1946.
- Hogeboom, G. H., Claude, A., and Hotchkiss, R. D.: *J. Biol. Chem.*, **165**, 620, 1946.

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DISCUSSION.—DR. WALTMAN WALTERS, Rochester, Minn.: I think we should all commend Doctor Firor for this excellent research of a type which few of us are in position to carry out but which he and his associates have done admirably.

As a member of the National Advisory Cancer Council I bring to your attention something which I think you should know. In 1937, Congress created the National Cancer Institute. The appropriation for this Institute has varied from \$400,000 to \$570,000 each year, until the current fiscal year in which it was increased to \$1,772,000. These figures are used for the support of the National Cancer Institute and the various grants-in-aid recommended by the National Advisory Cancer Council. Dr. George Smith of New Haven, Dr. Frank Adair of New York, Doctors Ivy and Huggins, Dr. Sherwood Moore of St. Louis, Dr. Robert Stone of San Francisco and I are members of the committee which meets with the Surgeon-General of the United States Public Health Service and with Dr. R. R. Spencer of the National Institute of Health. This agency operates the National Cancer Institute in which some of the investigations of cancer are being carried out. Other studies are being made in leading medical institutions of this country. These monies are available for use in the study of any problem associated with cancer.

Some of you may say that you have not sufficient trained personnel in your hospitals

to carry out investigations of cancer. You will be interested in knowing of the type of grants requested and that many of the studies needed could be carried out by any of us. For example, studies dealing with (1) the frequency with which gastric polypi become cancerous; and (2) the incidence of cancer in presumably benign gastric lesions as well as in the presence of atrophic gastritis are being carried out in one institution. At a recent meeting of the Western Surgical Association, Lt. Col. Frank E. Hamilton, of Walter Reed Hospital, presented a report of the effect on the stomach of roentgen therapy applied to the abdomen for treatment of metastatic tumors of the testis. Chronic perforating gastric ulcers resulted.

Studies of this type can be carried out by all of us if we have the opportunity. We were told that in the next session of Congress, as a result of demands from people all over the country, an appropriation of \$100,000,000 will be sought for the study of cancer. The plan is to bring scientists from all over the world to the United States in an effort to correlate and to further projects of research on cancer in accordance with plans to be developed by these men in a manner similar to that used in invention of the atomic bomb.

My suggestion would be that those who desire to carry out research on cancer do something which we, as scientists and doctors, find difficult to do; namely, request our senators or representatives in Congress to see that this money is wisely spent, make suggestions as to the types of research on cancer that might be carried out and request grants of money for support of such studies in our medical schools and hospitals. I should like to encourage all who have any desire to do research on cancer to make inquiry of the National Advisory Cancer Council as to what monies are available for such purpose.

DR. JOHN C. A. GERSTER, New York City: Now that the country has become cancer-conscious there is much danger of confusion and duplication of effort. The hundred million dollar Bill mentioned by Doctor Walters is a good example of this because, while authorizing appropriation of this sum for the commendable object of gathering scientists from all over the world to attack the cancer problem, it seems so loosely written—lacking any proper directive provisions—as to be almost a blank check and, thus, open to great political distortion. Obviously for this reason the Bill is now being rewritten.

The government is fighting cancer; I understand some \$200,000 of federal money is available for New York State alone. The American Cancer Society also has substantial funds allocated for cancer work in this same territory. A year ago the American Cancer Society, whose three-fold object is research, service and education, collected four and a quarter millions from all over the country. They engaged the National Research Council of the National Academy of Sciences' Committee on Growth to pass on all research problems submitted and to recommend action on these back to the American Cancer Society. There are 19 separate panels of the Committee on Growth to conduct and supervise research on every aspect of the cancer problem.

This year the American Cancer Society's campaign grossed more than 11,000,000 dollars.

Now for some of the confusion: The National Cancer Institute of the U. S. Public Health Service is located at Bethesda, Maryland, with Dr. Roscoe Spencer as its head; on the other hand, the National Cancer Foundation is a well-intentioned organization directed mainly toward terminal care of the advanced cancer patient. While this is a most worthy charity, it, alone, is not going to solve the main problem. To concentrate everything on advanced cancer care is like pouring money down a rat hole. This well-intentioned movement should not be confused with more worthy organizations which, *while including advanced cancer care in their programs*, stress the clinical and basic research aspects of the cancer problem as the only path toward the light!

DR. CHAMP LYONS, New Orleans, La.: I am sure we are all filled with admiration for this magnificent achievement in pathologic research. One of the most remarkable

PHASE DIFFERENCE MICROSCOPY

aspects of this accomplishment is the opportunity provided for testing new drugs as competitors with essential metabolites in the enzyme systems of neoplastic cells. Doctor Firor has carried the technic to a high degree of perfection. I should like to ask him to briefly outline his technic.

DR. WARFIELD M. FIROR, Baltimore (closing). I want to thank Doctor Walters and Doctor Gerster for their timely remarks. I heartily endorse everything Doctor Gerster said about the need for thinking clearly and not confusing these various agencies. In answer to a question asked me personally, as to the speed at which these exposures were taken, one can say that this varies according to cell activity; roughly one exposure every $\frac{1}{10}$ second. Many times one has to watch a cell for four or five hours before it begins to divide.

In answer to Doctor Lyons; I think I might make clear the essentials of phase microscopy by using the blackboard. If one has a light source here, and here an object; here is the microscope with the objective lens, and here the resulting image. This image will be altered by certain variables or variations in the components of the object. First, the ability of different parts of the object to transmit light; second, the thickness of the components of the object; third, the index of refraction of these components. If in this object there is a highly refractile granule, that will be reflected in the image. The product of the thickness times the index of refraction divided by the wave length is called optical path. The optical path, expressed in wave lengths γ is equal to nt/γ where t is thickness and n is the index of refraction of the structure. When optical path differences between adjacent parts of the object are very great, one can get a sharper image by dark-field illumination. When, however, there is very slight difference in the thickness or in the index of refraction of material that goes to make up the object, one can not detect these differences with the ordinary light microscope, and under these conditions phase microscopy is particularly helpful. This method consists of putting into an objective lens a disk of glass on which there has been evaporated a metallic or dielectric material which absorbs some of the rays of light, or deflects them. Some 60 different plates have been devised.

Obviously, the possibilities of this method are very great. For a technical presentation of phase microscopy one is referred to a paper by Bennett,² *et al.*

SURGICAL CONSIDERATIONS IN THE TREATMENT OF HYPERTENSION*

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THE SURGICAL TREATMENT of hypertension by means of extensive sympathectomy and splanchnicectomy has been accepted as a sound and logical physiologic procedure. It is true that abnormal elevation of the blood pressure may persist for years in a mild degree without producing symptoms or disability, so that neither medical nor surgical treatment is indicated. More severe elevation of blood pressure may respond to medical management and remain under control without proving disabling or showing evidence of progression. In reviewing reports relating to the surgical treatment of hypertension, one is struck with a universal problem confronting the medical profession; namely, the control of progressive hypertension or the alleviation of distressing symptoms of an already severe and serious hypertension.

Various types of sympathectomy have been carried out and studied extensively, both preoperatively and postoperatively, and from these we have learned much about what can be accomplished by each type of procedure. In contrast to many operations performed on man which have as their principle the removal of pathologic tissue, the operative treatment of hypertension is based on a physiologic response of the patient; that is, interruption of the sympathetic fibers will abolish or diminish the increased arteriolar tone in the lower half of the body. As Grimson¹ has stated, the lowering of the blood pressure observed to follow sympathectomy has been directly proportional to the extent of the sympathectomy and inversely proportional to the severity of the disease.

CLASSIFICATION

Due to the fact that the clinical syndrome which we have come to recognize as hypertension has no single etiologic factor and that elevated blood pressure associated with arteriolar changes may result from many combinations of causes, it is necessary to have a clinical classification as a basis for evaluation of therapeutic results and for prognosis. Several classifications have been developed by the various workers in this field, based on the apparent clinical and pathologic evidences of the severity of the disease. All classifications have a common objective in evaluation of the severity of the disease as well as in the selection of patients whose condition should respond satisfactorily to surgical treatment.

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TREATMENT OF HYPERTENSION

Hypertension may be divided into two main groups: (1) secondary; and (2) essential or primary hypertension. Secondary hypertension results from such lesions as glomerulonephritis, pyelonephritis, obstruction of the urinary tract, rare conditions obstructing a renal artery, polycystic disease, terminal periarteritis nodosa and disseminated lupus, coarctation of the aorta and tumors of the suprarenal and pituitary glands.

It is not our purpose to discuss this group at length; however, it seems advisable to call attention to the unilateral renal lesions, usually atrophic pyelonephritis (contracted kidney), which may be causes of hypertension. This type of lesion is of importance to the surgeon, since there are an increasing number of reports of favorable responses to removal of such lesions. However, these favorable responses actually are comparatively rare.

When this lesion has been suspected, it is customary at the Mayo Clinic to have a combined operation performed by the urologic and neurologic surgeons, the operation consisting of nephrectomy and sympathectomy. The two operations can be carried out through the same incision without materially increasing the operative risk. If definite and persistent lowering of the blood pressure occurs after removal of the kidney, further surgical treatment (sympathectomy on the opposite side) is not necessary. In such circumstances removal of the kidney is given credit for the lowering of the blood pressure, for it is known that unilateral sympathectomy does not materially lower the blood pressure for more than a few days. If, a week or ten days after removal of an atrophic kidney is performed in association with sympathectomy, there is no decrease in blood pressure, it is assumed that the kidney is not the sole etiologic factor, and a secondary operation is then considered necessary. The patient is then regarded as having primary or essential hypertension.

ESSENTIAL OR PRIMARY HYPERTENSION

Etiologic Factors.—Not much is known about the mechanism of elevation of the blood pressure in the presence of essential hypertension. Three factors are responsible for maintenance of normal blood pressure, and derangement of any one of these may cause a change in the blood pressure. The factors in question are: (1) the cardiac output; (2) the volume and viscosity of the blood; and (3) the resistance offered to the flow of the blood through the peripheral parts of the arterial system. It has been proved that cardiac output or viscosity of the blood is not altered in cases of essential hypertension, but that the caliber of the peripheral vessels is decreased. The decrease in diameter of the peripheral vessels is attributable to (1) a condition inherent in the arterioles; and (2) an abnormal reaction of the arterioles to vasomotor stimuli. Wide fluctuations of blood pressure would be indicative of an abnormal response of arterioles to vasomotor stimuli. A high sustained blood pressure with little fluctuation would be indicative of an inherent or automatic constriction of the arterioles.

There is a large hereditary factor in essential hypertension, as revealed by Ayman² (1934), who found that in families in which both parents had absolutely normal blood pressure, the incidence of elevated blood pressure among

the children was only 3 per cent. In families in which one parent had hypertension the incidence increased to 28 per cent, and in families in which both parents had arterial hypertension the incidence was 45 per cent. Hines and Brown³ have shown that a familial history of hypertensive cardiovascular disease is five times more frequent among persons who have hypertension or who are hyperreactive to a standard stimulus (immersion of the hand in ice water) than it is among persons who react normally to the test. The exact inherent quality responsible for this is not known, but probably a hyperreacting sympathetic nervous system responds abnormally and produces unusual vasoconstriction as a result of various emotional stresses and strains. This, in turn, may lead to so-called neurogenic hypertension.

Classification of Primary or Essential Hypertension.—We have assumed that in any attempt to assess the value of an operative procedure for hypertension, the results of surgical treatment must show a decided improvement over those of medical treatment. Because, since 1932,⁴ a classification has been used at the Mayo Clinic in the diagnosis and medical treatment of hypertension, we have used this classification as a guide and yardstick in evaluation of our surgical results. Keith, an internist, and Wagener, an ophthalmologist, with the collaboration of members of the sections on vascular diseases and pathologic anatomy, have followed an unusually large number of patients suffering from hypertension over a period of two decades or more and have accumulated, therefore, a vast amount of clinical and pathologic material on the basis of which their classification has been developed.

They have classified essential hypertension into four groups.⁵ To avoid the use of descriptive terms, the groups have been given numbers: (1) slight to moderate increase in the blood pressure, which ordinarily becomes normal as a result of rest, and mild sclerosis of the retinal arteries, usually without symptoms (Fig. 1a); (2) moderate to severe hypertension, moderate sclerosis of the retinal arteries, and occasionally venous thrombosis; clinical symptoms are present or absent (Fig. 1b); (3) moderately severe hypertension and angiospastic retinitis with an exudative retinopathy almost always associated with clinical symptoms of hypertension (Fig. 1c); and (4) severe hypertension, angiospastic retinitis, edema of the optic disks and, always, clinical manifestations of hypertension (Fig. 1d).

This grouping does not indicate the degree of hypertension, although the blood pressure is often higher in one group than in the group which numerically precedes it. The hypertension of any patient may progress from group to group until Group 4 is reached. The fatality rate among patients who have hypertension of Group 1 or Group 2 is 30 to 42 per cent, respectively, within four years. The fatality rate among patients who have hypertension of Group 3 is 78 per cent within four years, and in Group 4 the rate is 98 per cent (Keith, Wagener and Barker⁶). This high fatality rate should be noted carefully by those who are inclined to consider that hypertension ordinarily is not a serious disease. Malignant hypertension and essential hypertension are not separate conditions, for malignant hypertension is a type of essential hyper-

tension. The term "malignant" is used loosely to designate severe forms of hypertension.

This classification may be unsatisfactory because it fails to indicate the importance of the rapidity of progression of the disease. As a working basis, however, the classification is acceptable, since the seriousness of hypertension ordinarily increases progressively as the number of the group into which it is classified increases. Thus, to be of clinical value, the surgical treatment of hypertension must show control of the progress of the disease from one group to another, or a lessening in the severity of the hypertension.

Medical Treatment.—The medical treatment of mild essential hypertension usually is satisfactory, but severe hypertension frequently may not respond to medicine and diet. Some patients who have moderate hypertension of Group 2 or 3 respond rather well, for a time, to medical treatment. A nontoxic, adequate and prolonged vasodilator would solve the problem of the treatment in many cases. The nitrites, acetylcholine series, histamine and two newer drugs, tetra-ethyl-ammonium chloride and the bromide salt of this compound, have in common a vasodilating action. The latter two drugs are now under investigation to determine their efficacy from the standpoint of selection of patients for surgery and the medical treatment of hypertension. Due to their temporary physiologic effect, their therapeutic value is questioned. There is some evidence that potassium thiocyanate may be effective (both before and after operation), but the dosage must be carefully regulated. The sedative agents, particularly the barbiturates, are the most valuable drugs. The amount of sedative drug should be great enough to abolish nervousness and restlessness and small enough to avoid drowsiness and excessively slowed mental reactions.

Surgical Treatment.—Although it is true that mild hypertension may persist for many years without evidence of progression, there are a large number of patients who come for surgical treatment after their condition has progressed to severe hypertension, with irreversible changes in the vascular tree of the heart, kidneys, brain and other organs. As was the case in the treatment of cancer 20 years ago, under the present setup we are attempting to alleviate symptoms produced by organic changes far beyond the scope of physiologic surgery. To us the answer thus far is early surgical attack, and our results in hypertension of Groups 1 and 2 as compared with those in hypertension of Groups 3 and 4 for the most part substantiate this recommendation.

Selection of Patients.—The postoperative results have revealed that a high fixed hypertension associated with diffuse arteriosclerosis is accompanied by irreversible changes throughout the body. Patients thus afflicted are not materially benefited by operation. For this reason, certain criteria have been sought by means of which it will be possible to predicate the postoperative results. Observation of the patient at rest and of his response to anesthesia, as well as sedation with the barbiturates, have been tried with varying results. Comparison of the results obtained in the various groups of hypertension, both before and after operation, have shown that patients suffering from severe hypertension in the later stages of the disease may not display marked clinical

improvement after surgical treatment. It is the consensus that patients more than 50 years old with a high diastolic pressure should be looked on as poor operative risks for whom only questionable results can be obtained. Patients who have maintained a high pressure over a long period of time often prove refractive to surgical treatment. It has been found experimentally and clinically that the blood-pressure-altering effect of rest, sedation and anesthesia has been variable. Causative factors or surgical prognosis based principally on rest and the use of sodium amytal or the results of anesthesia tests may be misleading.⁷ The blood-pressure-lowering effect of these tests clinically should be but one of the many factors considered in evaluation of the condition of the hypertensive patient.

Types of operation for hypertension are listed in Table I.

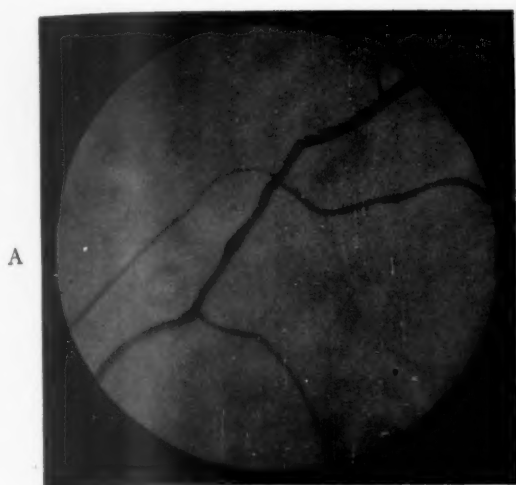
Surgical Operation.—The multiplicity of operations⁸⁻¹⁷ which have been tried and the controversy which has been aroused in respect to the application and results are testimony, in themselves, that one procedure has not proved to be infallible.

All operations for the relief of essential or primary hypertension have a basic physiologic objective consisting of denervation of the vascular tree of the abdominal viscera and the lower extremities. All operative procedures take cognizance of the fact that failure results if both cardiac and renal functions are significantly impaired. Irreversible changes in the vascular, muscular and nervous systems, as well as in the cardiac, renal and other vital organs, indicate a condition which is not amenable to this physiologic type of operation.

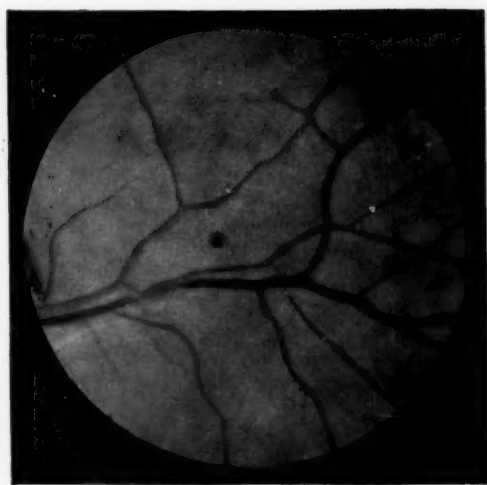
Thus far, in review of the results of operation in the treatment of hypertension, it is evident that two types of responses are significant. In one group of cases there has been a definite control of the progression of the disease as evidenced by a lowering of both the systolic and the diastolic pressure for varying periods. In another group there has been a decided relief of the distressing and disabling symptoms without a startling lowering of the blood pressure. This is true in spite of the definite objective of lowering the blood pressure primarily and relieving the symptoms secondarily.

In the acquisition of experience with the different operative procedures, with careful preoperative and postoperative studies of the patients and a longer period of observation, much has been learned, and it is important to realize that the surgical treatment has brought out many hitherto unknown physiologic facts about the disease.

In view of the fact that all the procedures in question have been followed by some alleviation of elevated blood pressure and symptoms and are attended with a low fatality rate (with the exception of the several types of rhizotomy^{8, 9} which have been abandoned), it is barely possible that they can be used individually in the treatment of various phases or stages of hypertension. This has proved to be true in many controversial operative surgical procedures in general surgery and the other surgical specialties. In fact, in our combined medical and surgical departments we have discussed this problem and are, at the time of this report, comparing the results of various operations in the hope



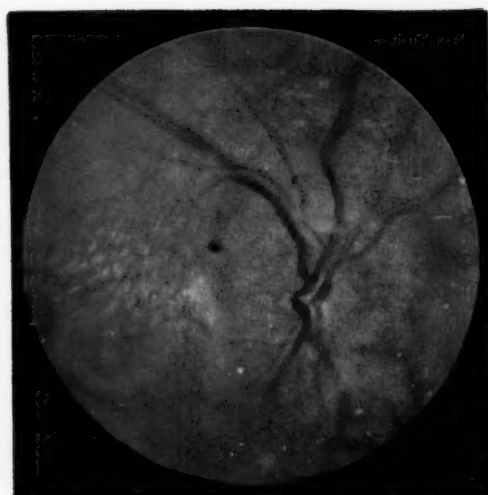
A



B

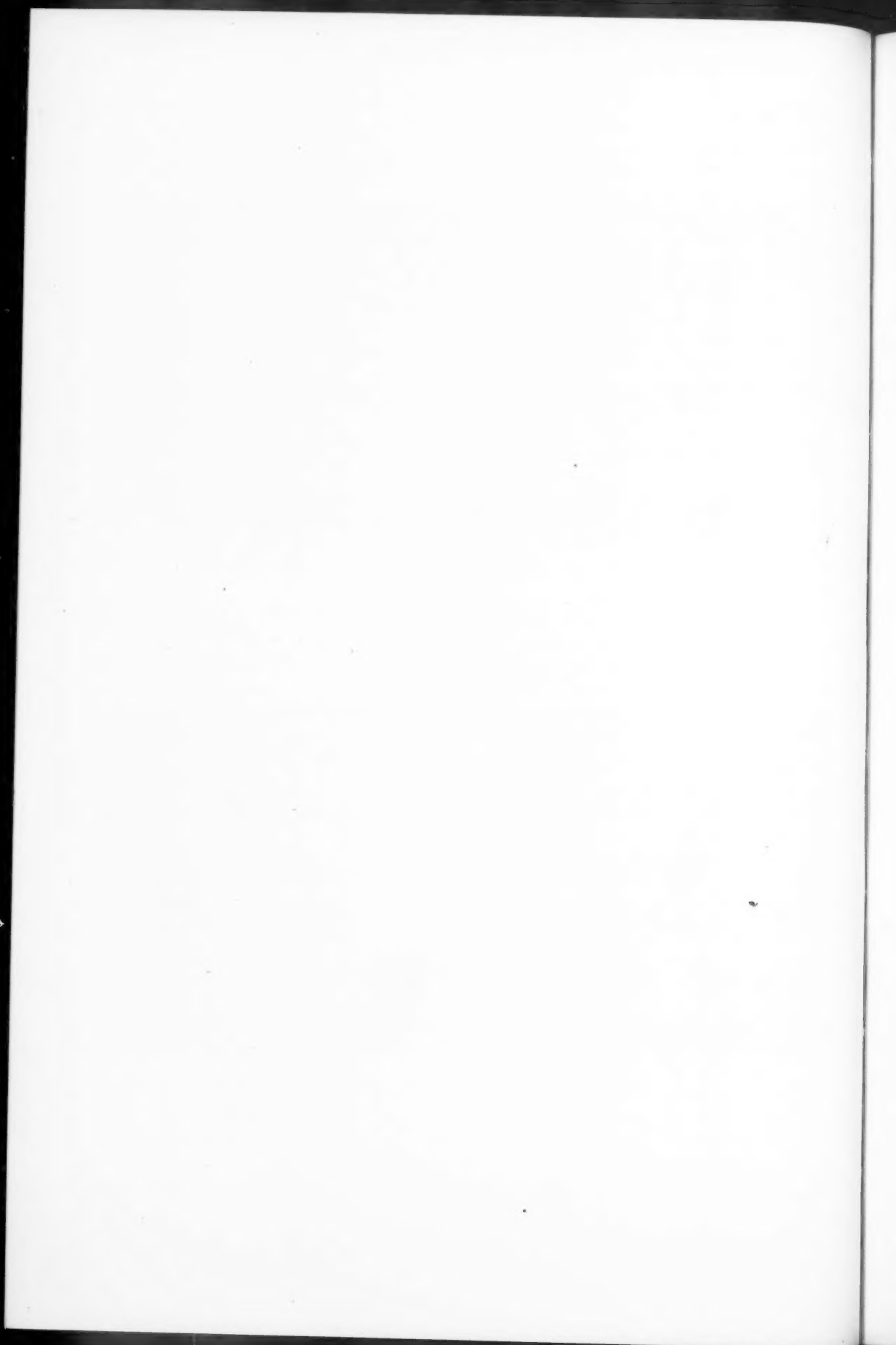


C



D

FIG. 1 (A).—Diffuse arteriolar disease with hypertension of group 1, generalized narrowing of grade 1, and chronic sclerosis of grade 1 of the retinal arterioles; (B), diffuse arteriolar disease with hypertension of group 2, generalized narrowing of grade 1, and chronic sclerosis of grade 2 of the retinal arterioles; (C), diffuse arteriolar disease with hypertension of group 3, retinopathy without papilledema, a cotton-wool patch and hemorrhage and residues of edema in the retina; (D), diffuse arteriolar disease with hypertension of group 4, retinopathy with papilledema and partial macular star. (Original colored photographs from the collection of Drs. H. P. Wagener and C. W. Rucker and reproduced through their courtesy.)



of clarifying this question. However, it will take a longer period of observation and study of the patients who have undergone the more extensive sympathectomy before any valid conclusions can be made.

Surgical Technics.—So much has been written concerning the different technics that it seems unnecessary to refer to them in detail. So many contributors have been involved that, in the hope of presenting a brief review, we have assumed that too many names would confuse the subject.

Suffice it to say that rhizotomy extending from the 6th thoracic nerves to the 2nd lumbar nerves was carried out with the idea of interrupting the sympathetic impulses to the splanchnic vessels and the vessels of the lower extremities.⁸ Physiologically, this was sound, but the procedure also involved the motor components of the spinal nerves, which only beclouded the picture, and the operation proved to be of such magnitude and to be accompanied by so much risk, not only of life but of physical disability, that it was abandoned as being surgically hazardous. However, before this procedure was abandoned, it was modified to involve the 9th thoracic nerve to the 2nd lumbar nerve, instead of the original 6th thoracic nerve to the 2nd lumbar nerve.⁹ Some gratifying results were obtained from the latter procedure without the extensive operation and the risk of the former. This showed that in some cases a modified procedure was effective.

The various types of rhizotomy, having proved that interruption of the sympathetic impulses to the splanchnic area was followed by a lowering of the blood pressure and a relief of symptoms, aroused the interest of neurosurgeons in approaching the problem from extraspinal route, and from this interest two procedures developed. Intrathoracic supradiaphragmatic resection of the 10th, 11th and 12th thoracic sympathetic ganglia and the intervening trunk, along with a corresponding section of the splanchnic nerves, has been carried out and several large series of patients have been followed for a period of years.¹² The results as reported are impressive, in respect to both lowering of the blood pressure and alleviation of symptoms.

The subdiaphragmatic operation, consisting of removal of the splanchnic nerves and the 1st and 2nd lumbar sympathetic ganglia with the intervening trunk, has been carried out in large series, with results which show a definite advance in the surgical treatment of hypertension.^{10, 11} The patients concerned have been studied both preoperatively and postoperatively over a period of years, and the results of such studies prove without a doubt that in some cases there has been a definite physiologic response to this type of denervation.

Under this impression—that both the supradiaphragmatic and the subdiaphragmatic types of resection of the splanchnic nerves and the sympathetic ganglia had their advantages, and that more extensive denervation probably would be followed by a greater response—the two procedures were combined into the transdiaphragmatic type of surgical procedure.¹³ This procedure has been modified by several surgeons^{14, 17} until now it has been accepted as a procedure which may be applicable to a group of patients whose condition did not respond as well as had been hoped for when the other procedures were

used. The first investigator (Smithwick)¹³ who combined the two procedures developed a technic consisting of removal of the 12th rib, division of the diaphragm and removal of the splanchnic nerves from the midthoracic region to the celiac ganglion and the sympathetic trunk from the 9th thoracic nerve to the 2nd lumbar ganglion. This operation was attended with a little higher fatality rate (2.8 per cent), but seemed to procure greater denervation than the others and to produce a more lasting postural hypotension. In a high percentage of cases this operation was followed by a lowering of both the diastolic and systolic blood pressures. This approach has been extended to include resection of other ribs and removal of the splanchnic nerves and sympathetic ganglia from the 1st thoracic nerve to the 5th lumbar ganglion in one series,¹⁶ from the 3rd thoracic nerve to the 2nd lumbar ganglion in a second series,¹⁴ and from the 7th thoracic to the 2nd lumbar ganglion in a third series.¹⁷

Thus, have developed the different types of operation for denervation of the so-called splanchnic vascular bed and the vessels of the lower extremities. There is no doubt that the more extensive types of denervation¹⁴⁻¹⁶ have their advantages, but there are also disadvantages. It has been proved, both experimentally and clinically, that too extensive resection of the sympathetic nervous system is followed by changes in certain functions subservient to these nerves. After the performance of quadrilateral sympathectomy for the relief of vascular disease such as thrombo-angiitis obliterans and Raynaud's disease, there is an absence of sweating in all extremities, so that the burden of bodily sweating is placed on the unaffected area. This is true in the case of performance of more extensive resection of the thoracic and lumbar sympathetic ganglia and, even though the response relating to the hypertension may be superior, the comfort of the patient must be considered, especially those patients who live in a warm climate or even those who live in a changing climate. Excessive sweating of any part of the body can be disabling and incapacitating, as evidenced by patients suffering from hyperhidrosis.

COMMENT

The surgical treatment for the relief of hypertension has passed through the stage of radical rhizotomy into that of extraspinal resection of the splanchnic nerves and the thoracic and lumbar sympathetic ganglia and trunks.

Classification and grouping of the disease have been chosen arbitrarily for a comparison between the medical treatment, on the one hand, and various types of surgical procedures, on the other. No satisfactory single criterion for the prediction of successful operations has been developed. It has been agreed that even the most extensive of the operations cannot change the clinical status of hypertension which has advanced to the degree of irreversible changes in the vessels of the heart, kidneys, brain and other organs.

The nature of the operation is physiologic rather than pathologic and the results depend on the physiologic response of the vascular system. All types of sympathectomy and splanchnicectomy have been followed by arrest of the progress of the disease and alleviation of symptoms. Although it is true that the more extensive operations have resulted in greater denervation of the

TREATMENT OF HYPERTENSION

vascular system, they also result in a more extensive cutaneous area of non-sweating which produces discomfort to the patient in adjusting to climatic changes, and further discomfort is experienced because of excessive sweating in the unaffected areas.

White¹⁸ has aptly summed up the present status of the surgical treatment of hypertension as follows: "Although it is not yet established that the results will be permanent, at least there is good reason to believe that the hands of the clock can be set back for a number of years in the majority of younger patients with hypertension who have not been permitted to progress to the stages of advanced degeneration or changes in heart, kidney or brain."

TABLE I
VARIOUS TYPES OF SURGICAL OPERATIONS FOR HYPERTENSION

- I. Rhizotomy:
 - a. Intraspinal division of anterior or motor roots of 6th thoracic nerve to 2nd lumbar nerve.¹
 - b. Intraspinal division of anterior or motor roots of 9th thoracic nerve to 2nd lumbar nerve.¹
- II. Sympathectomy and splanchnicectomy:
 - a. Subdiaphragmatic, 1st and 2nd lumbar sympathetic ganglia.^{10,11}
 - b. Supradiaphragmatic, 10th, 11th and 12th thoracic sympathetic ganglia.¹²
 - c. Transdiaphragmatic, 9th thoracic nerve to 2nd lumbar ganglion.¹³
 - d. Transdiaphragmatic, 3rd thoracic nerve to 2nd lumbar ganglion.¹⁴
 - e. Combined subdiaphragmatic and supradiaphragmatic:
 1. 1st thoracic nerve to 4th and 5th lumbar ganglia.^{15,16}
 2. 7th thoracic nerve to 2nd lumbar ganglion.¹⁷

REFERENCES

- ¹ Grimson, K. S.: The Surgical Treatment of Hypertension: Collective Review. *Internat. Abstr. Surg.*, **75**, 421-434, November, 1942.
- ² Ayman, David: Heredity in Arteriolar (Essential) Hypertension: A Clinical Study of the Blood Pressures of 1,524 Members of 277 Families. *Arch. Int. Med.*, **53**, 792-802, May, 1934.
- ³ Hines, E. A., Jr., and Brown, G. E.: The Hereditary Factor in the Reaction of Blood Pressure to a Standard Stimulus (Cold): Preliminary Report. *Proc. Staff. Meet., Mayo Clin.*, **10**, 371-373, June 12, 1935.
- ⁴ Keith, N. M.: II. Cardiovascular Diseases in Relation to the Retina. *Tr. Am. Acad. Ophth.*, **37**, 37-49, 1932.
- ⁵ Wagener, H. P., and Keith, N. M.: Diffuse Arteriolar Disease, with Hypertension and the Associated Retinal Lesions. *Medicine*, **18**, 317-430, September, 1939.
- ⁶ Keith, N. M., Wagener, H. P., and Barker, N. W.: The Problem of Prognosis in Essential Hypertension: A Follow-up Study in 219 Cases. *Tr. A. Am. Physicians*, **53**, 81-87, 1938.
- ⁷ Grimson, K. S., Kernodle, C. E., Jr., and Hill, H. C.: Hypertension: The Effect of Activity, Rest, Natural Sleep, Sodium Amytal, Pentothal Sodium, Chloralose and Ether on Experimental Neurogenic Hypertension and of Rest and Sodium Amytal and Anesthesia on Hypertensive Patients. *J. A. M. A.*, **126**, 218-221, September 23, 1944.
- ⁸ Adson, A. W., and Brown, G. E.: Malignant Hypertension: Report of Case Treated by Bilateral Section of Anterior Spinal Nerve Roots from the 6th Thoracic to the 2nd Lumbar, Inclusive. *J. A. M. A.*, **102**, 1115-1118, April 7, 1934.
- ⁹ Brown, G. E., Craig, W. McK. and Adson, A. W.: The Treatment of Severe Essential Hypertension; Effects of Surgical Procedures Applied to the Sympathetic Nervous System. *Minnesota Med.*, **18**, 134-138, March, 1935.
- ¹⁰ Adson, A. W.: Essential Hypertension: A Report of the Results Obtained by Bilateral Ventral Rhizotomy (6th Thoracic to 2d Lumbar Roots) and Bilateral Resection of Splanchnic Nerves. *J. Nerv. & Ment. Dis.*, **82**, 190-193, August, 1935.

- ¹¹ Adson, A. W., Craig, W. McK. and Brown, G. E.: Surgery in Its Relation to Hypertension. *Surg., Gynec. & Obst.*, **62**, 314-331, February, 1936.
- ¹² Peet, M. M.: Splanchnic Resection for Hypertension; A Preliminary Report. *Univ. Hosp. Bull., Ann Arbor*, **1**, 17-18, June, 1935.
- ¹³ Smithwick, R. H.: A Technique for Splanchnic Resection for Hypertension; Preliminary Report. *Surgery*, **7**, 1-8, January, 1940.
- ¹⁴ Hinton, J. W., and Lord, J. W., Jr.: Operative Technique of Thoracolumbar Sympathectomy. *Surg., Gynec. & Obst.*, **83**, 643-646, November, 1946.
- ¹⁵ Grimson, K. S.: The Sympathetic Nervous System in Neurogenic and Renal Hypertension; Experimental Correlation and Clinical Consideration. *Arch. Surg.*, **43**, 284-305, August, 1941.
- ¹⁶ Grimson, K. S.: Total Thoracic and Partial to Total Lumbar Sympathectomy and Celiac Ganglionectomy in Treatment of Hypertension. *Ann. Surg.*, **114**, 753-775, October, 1941.
- ¹⁷ Poppen, J. L.: Technic for Supradiaphragmatic and Infradiaphragmatic Sympathectomy for Hypertension. *Lahey Clin. Bull.*, **3**, 151-158 (July) 1943; Correction in **3**, 187, October, 1943.
- ¹⁸ White, J. C.: Progress in Surgery of the Autonomic Nervous System, 1940-1942. *Surgery*, **15**, 491-517, March, 1944.

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DISCUSSION.—DR. FRANK H. LAHEY, Boston, Mass.: I wish to disclaim any experience with operations for hypertension, but as I said to Doctor Craig, one of the most important things a clinic such as ours can do is to report our end-results as often as possible in these cases in order that we may determine what to expect from them. It is essential that the end-results of the various operations for hypertension be put on record as soon as possible, and in as significant numbers as possible.

These are the results in 100 consecutive cases in which operation was carried out in the neurosurgical department by Dr. James L. Poppen and the patients' course followed from one and one-half to four years. These results are being reported by Doctor Poppen in a paper sent to the Journal of the American Medical Association. All these patients have had one type of operation, a technic devised by Doctor Poppen in which he removes the thoracic and lumbar sympathetic chain in continuity from the fourth dorsal to the second lumbar ganglia, inclusive. This is accomplished by the removal of a small segment of the medial portion of the 11th rib and also the 7th or 8th rib depending on the amount of lordosis of the thoracic spine. A paper on the technic employed is in press. Doctor Poppen has tried to divide these results into "good," "fair" and "unsatisfactory." A good result is to be expected when, after operation, the maximum blood pressure is 150 mm. systolic and 100 mm. diastolic, the patient is in good physical condition and relieved of all symptoms associated with hypertension. Doctor Poppen has found, as Doctor Craig has, that there is no test by which one can predict in which case there will be a good result, and I am sure that everyone is anxious to get some test to determine that. It is not possible to select these cases by the blood pressure alone. They have determined not only the blood pressure in the cases in which the results are classified as fair, poor and unsatisfactory but have included, also, the reversal of electrocardiographic findings, roentgenologic evidence of change in the size of the heart and improvement in the arterioles of the retina and subjective symptoms. These they have placed last, as of the least significance.

In these cases the results have been good in 47 per cent, fair in 24 per cent and unsatisfactory in 22 per cent. The mortality has been 0.5 per cent. It is interesting in interpreting these findings that there has been a drop in blood pressure in 71 per cent, but in some of these there have not been associated satisfactory changes of the character I spoke of (such as the roentgenogram of the heart and the electrocardiogram, etc.) and so they have not been included in the satisfactory group.

TREATMENT OF HYPERTENSION

Doctor Poppen in the follow-up of his group of cases has ascertained the effect of this operation upon sexual power. This is one of the important things we have to tell male patients before operating upon them by this plan. We all know the relationship of the lumbar ganglia and their influence upon the ejaculation power and it has been of interest to know what the effect has been. Fifty-eight per cent of this group were females, 42 per cent were males. Of these latter, 41 per cent had normal ejaculation after operation and 21 had no ejaculation, and in 18 per cent the power of ejaculation was diminished. It is also important to note what the effect has been on libido or potency, and Doctor Poppen reports that it is the same in 65 per cent, diminished in 23 per cent, and here is a strange fact concerning the question of the complete control of the power of ejaculation by the 1st or 2nd lumbar ganglion—libido and potency were improved in 12 per cent. In women there has been no change, and there have been pregnancies in some of the cases.

Since this is a group of patients operated upon by the same individual by the same technical plan and followed from one and one-half to four years, we thought it would be valuable to present them in relation to Doctor Craig's paper.

DR. LOYAL DAVIS, Chicago: In 1939, Dr. Marion H. Barker and I presented before this Association our experiences with the surgical treatment of patients with hypertension, by removal of portions of the sympathetic nervous system. Deliberately, we confined ourselves to a study of those patients who had been treated by various medical measures without success, but, in particular, all the patients had been resistant to the administration of potassium sulfocyanate.

This group of patients had been under observation for from seven to ten years, and we are now engaged in compiling an accurate and meticulous survey of their present condition. Many of them are enjoying a satisfactory social and economic existence on the cyanate regimen who, without operation and the resulting sensitivity to cyanates, we believe would have succumbed to their disease. Our experience with cyanate therapy and with sympathectomy in cyanate-resistant patients has been supported by the findings in other clinics.

It is obvious that many, in fact, the majority of the patients with essential hypertension whom we see in the clinic, belong to the group who react satisfactorily to the cyanates when they are properly administered and controlled. We have not as yet subjected this group to operation, but it is our opinion that were we to do so, the results following sympathectomy alone would be comparable to those reported from other clinics. In fact, after using all the proposed preoperative tests to determine whether or not sympathectomy may benefit the patient, we have come to believe that the therapeutic test with the cyanates is the most reliable. In addition to our own patients, our experience with patients operated upon elsewhere who come under Doctor Barker's management, supports this tentative conclusion.

The cyanate-resistant patient with hypertension belongs to the most unpredictable group whose course may suddenly become fatal, but for the same reason they constitute the group for whom every possible therapeutic measure should be employed. By limiting our own investigations to a single group of clinically well-defined patients, we believe that the final evaluation of the surgical treatment of hypertension will be materially hastened, and we are hopeful that our clinics will add to our experiences with this group of patients.

DR. WINCHELL MCK. CRAIG, Rochester, Minn. (closing): I am extremely grateful for this discussion. As I stated, I was trying to bring out the problems of surgical treatment of hypertension. The remarks of Doctor Lahey and Doctor Davis have shown that we have kept in mind the effect on patients and, following the statement of Doctor Davis, we hope, in connection with laboratory studies and further pharmaceutical studies, to further the treatment of hypertension.

CHRONIC SHOCK: THE PROBLEM OF REDUCED BLOOD VOLUME IN THE CHRONICALLY ILL PATIENT*

PART I—CONCEPT OF CHRONIC SHOCK

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A REDUCED TOTAL QUANTITY of circulating blood in patients with nutritional deficiency was reported by Chang¹ in 1932. Similar observations in hypoproteinemic animals have been recorded in the reports of the experiments of Holman, Mahoney and Whipple,² and of Elman and Davey.³ In a study of patients with persistently unhealed war wounds, attention was directed to a syndrome characterized by weight loss, reduced blood volume and increased interstitial fluid volume.⁶ Diminished blood volume in debilitated patients has also been noted by Gregersen,⁴ and by Varco.⁵ All these reports emphasize the coincidence of protein depletion and diminished blood volume. The surgically significant feature of reduced blood volume is an increased susceptibility to shock correctable by transfusion replacement of the blood volume deficit.⁶ It is on this basis that it is proposed to designate the syndrome as "chronic shock."

Much of an admittedly controversial nature precludes immediate acceptance of this concept of a reduced blood volume attributable to depletion of body protein. On the other hand, it has been possible to integrate such a mechanism in orderly relationship to currently accepted physiologic processes. Four years' experience with the clinical application of this hypothesis has offered considerable proof of the fundamental integrity of the underlying teleologic deductions. It is the purpose of this series of papers to present the rationale and factual data upon which the syndrome of "chronic shock" has been postulated.

Starling⁷ described the mechanism whereby the hydrostatic force of the capillary blood pressure and colloid osmotic pressure of the plasma proteins effected an interchange of fluid across the semipermeable capillary wall. Schade,⁸ in an extension of Landerer's⁹ earlier concepts, added the factor of tissue tension as contributory to the return of fluid from the interstitial reser-

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CHRONIC SHOCK

voir to the vascular compartment. Tissue tension was accepted by Peters,¹⁰ and emphasized by Youmans,¹¹ as the only available mechanical force to supply a necessary increment of pressure. It is now recognized that some protein leakage across the capillary wall occurs normally.¹² The effective filtration forces of capillary blood pressure (BP), osmotic pressure of plasma protein (PP), tissue tension, or pressure (TE) and osmotic pressure of interstitial fluid protein (IFP) are diagrammatically summarized in Figure 1.

The usual distribution of the extracellular fluid is such as to maintain a ratio of plasma volume to interstitial fluid volume of 1:3.¹³ However, wide variation in the total quantity and apparent distribution of the extracellular fluid is known to occur.¹⁴⁻¹⁷ It has been concluded that these fluctuations maintain plasma volume through a reciprocal balance of the filtration forces mediated by the osmotic pressure of the plasma proteins and the tissue tension respectively.^{14, 16} This relationship is presented schematically in Figures 2, 3 and 4.

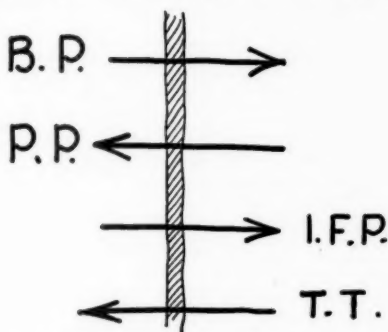


FIG. 1.—Diagrammatic representation of filtration forces across the capillary wall.

B. P., capillary blood pressure; P. P., osmotic pressure of plasma protein; I. F. P., osmotic pressure of interstitial fluid protein; T. T., tissue tension or pressure.

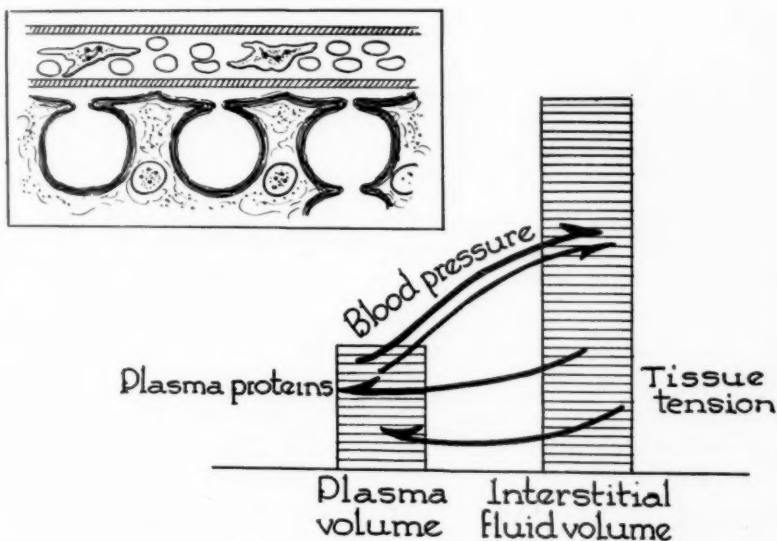


FIG. 2.—Diagrammatic representation of normal forces acting to maintain P. V. : I. F. V. ratio.

Failing of explanation within this concept are numerous clinical observations of increased interstitial fluid volume and decreased plasma volume, with

normal concentration of plasma proteins.^{4, 6, 15} In dogs maintained on a protein-inadequate diet or rendered edematous by plasmapheresis, edema has been noted in the absence of significant lowering of the concentration of plasma proteins.¹⁸ The persistence of a normal pattern of plasma protein concentration has been confirmed by Tiselius determinations upon the plasma

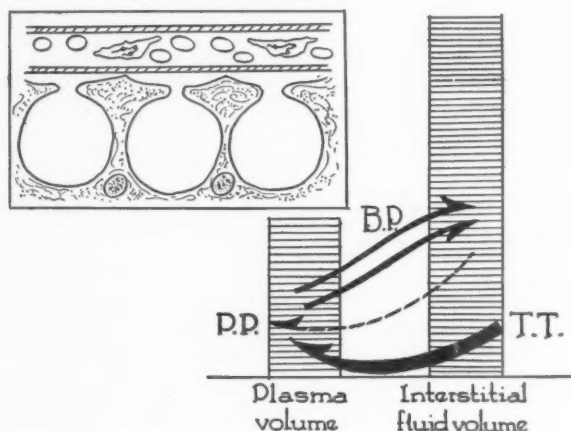


FIG. 3.—Diagrammatic representation of forces acting to maintain P. V. : I. F. V. ratio in sodium retention and hydremia.

B. P., capillary blood pressure; P. P., osmotic pressure of plasma protein; T. T., tissue tension or pressure.

TABLE I

PLASMA VOLUME—INTERSTITIAL FLUID VOLUME RATIO IN PATIENTS WITH DELAYED WOUND HEALING*

Patient	Weight Loss (Kg.)	Conc. of Plasma Prot. (Grams %)	Plasma Volume (Ml.)	Interstitial Fluid Volume (Ml.)	Ratio P.V.:I.F.V.
1.....	0	...	3,900	13,900	1:3.3
2.....	4.2	8.0	2,900	15,900	1:5.4
3.....	5.6	...	2,400	13,500	1:5.6
4.....	6.4	6.9	3,200	13,800	1:4.3
5.....	14.4	8.0	2,400	12,100	1:5
6.....	14.9	7.6	2,600	15,800	1:6
7.....	15.1	...	2,100	15,100	1:7.1
8.....	16.7	6.7	2,600	16,600	1:6.4
9.....	30.0	7.2	2,700	15,800	1:5.8

* The analyses were made by Miss Margaret Rourke by concomitant determinations of the plasma volume with the dye T-1824²⁰ and extracellular fluid volume with sodium thiocyanate²¹. Plasma proteins were determined by Kjeldahl analysis.

of human subjects with edema¹⁹ due to famine. Certain unpublished observations from a previous study⁶ are pertinent in this regard. The clinical subjects were soldiers depleted in consequence of prolonged exudation from persistently open war wounds. The findings are summarized in Table I. Alteration of the usual 1 : 3 ratio of plasma volume to interstitial fluid volume is the consequence of decrease in the plasma volume and increase of the interstitial

CHRONIC SHOCK

fluid volume. There is no real correlation between the amount of weight lost and the degree of alteration of the ratio, comparable changes being noted with a loss of nine pounds (Patient No. 2), and 65 pounds (Patient No. 9). As previously noted,⁸ there is correlation of reduced body weight, reduced plasma volume and reduced total mass of circulating blood proteins, both hemoglobin and plasma protein.

Schoenheimer's²² concept of the dynamic equilibrium of all the body proteins warrants the conclusion that protein depletion should affect tissue protein as well as blood proteins. It has now been shown that weight loss is correlated with reduced total mass of blood proteins even though the concentration of the blood proteins is not significantly altered. Masked deficiencies of this sort

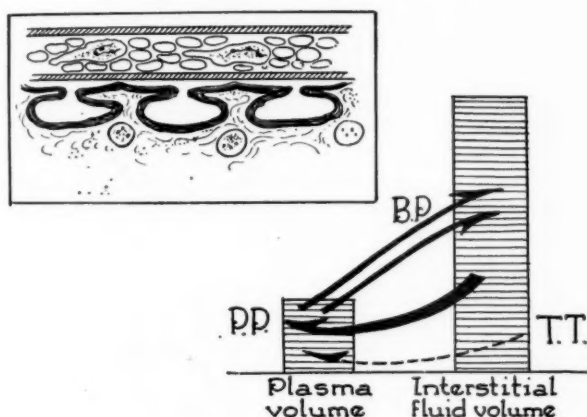


FIG. 4.—Diagrammatic representation of forces acting to maintain P. V.:I. F. V. ratio in dehydration and oligemia.

B. P., capillary blood pressure; P. P., osmotic pressure of plasma protein; T. T., tissue tension or pressure.

have been recognized previously.²³ Recognition of the factor of tissue protein depletion offers a mechanism whereby the interstitial fluid volume could expand as the result of reduced tissue tension associated with loss of some tissue protein, such as collagen.¹⁸ Loss of tissue tension implies that the quantity of the plasma volume is predetermined by the *hygroscopically active concentration* of a reduced total mass of plasma colloids. Such an explanation fits the factual data rather well. This postulated mechanism is presented in Figure 5. Other students of this problem have emphasized alteration of the physiologic integrity of the capillary wall.¹⁹ Robertson and Bock²³ found it impossible to restore blood volume beyond a certain point when further increase in plasma volume would, by dilution, have reduced the hemoglobin concentration percentage to a very low figure. Anemia, in consequence of reduced total mass of hemoglobin, has been shown to favor loss of fluid and protein from the vascular to the interstitial fluid compartment.²⁴

The exact mechanism whereby the recorded changes are produced is admittedly complex. Important for clinical emphasis is the observation that

in patients with weight loss the reduced plasma volume may mask deficiencies in the total mass of blood proteins. The significance of increased interstitial fluid volume remains to be elucidated.

DISCUSSION.—The concept of a state of "chronic shock" may be protested on several grounds. Gregersen, and others,^{4, 25, 26} have answered most of the theoretic and technical dissatisfactions with the method of blood volume determination. Criticism based on the known variation in the plasma volume among "normal" subjects²⁷ has been countered by consideration of the plasma volume

TABLE II
CONSTANCY OF THE PLASMA VOLUME IN NORMAL INDIVIDUALS

Date 1946	Subject			
	W. W.	W. N.	H. M.	R. K.
January.....	2,625		2,535	
February.....		3,515	2,750	
March.....			2,795	
April.....		3,335		
May.....	2,730			
June.....				3,130
July.....				
August.....	2,690			3,350

TABLE III
CHANGES IN WEIGHT AND BLOOD VOLUME DURING CONVALESCENCE

Date	Weight	Blood Volume
4/2/46.....	106 lbs.	3,400 ML.
5/9/46.....	83 lbs.	4,400 ML.
6/20/46.....	85 lbs.	4,600 ML.

Patient entered with carcinoma of stomach resected on 4/26/46. No postoperative transfusions were given. Weight prior to illness was 128 pounds. It should be noted that blood volume restoration and maintenance during convalescence reveals a deficiency of 1,200 ML. at the time of the initial blood volume determination.

to interstitial fluid volume ratio and by serial determinations of the blood volume in individual patients. Hematologists²⁸ are reluctant to accept a concept invalidating the hemoglobin concentration as an accurate index of the total quantity of circulating hemoglobin, although biochemists have long emphasized the fallacy of assuming that solute concentrations reflect the plasma volume.²⁹⁻³¹

The constancy of the plasma volume, as demonstrated by serial determinations in a series of given individuals, is attested in Table II. The presence of reduced blood volume in a patient with weight loss is confirmed by the demonstration of restoration of blood volume to a higher level during convalescence (Table III). It has been repeatedly observed that restoration of the blood volume precedes significant recovery of weight during recuperation from debilitating illness. Methods of evaluating the blood volume deficit in

CHRONIC SHOCK

patients with weight loss and the quantitative aspects of transfusion restoration of blood volume will be reported subsequently.

Clinical practice in the restoration of structural defects of the extracellular fluid has been based on Gamble's¹³ demonstration of the ability of the normal kidney to retain selectively the needed electrolyte. Quite recently, Collier, and coworkers,³² challenged this established program by presenting evidence of excessive retention of water, sodium and chloride in patients with sound kidneys and normal concentrations of the plasma proteins. The subjects of

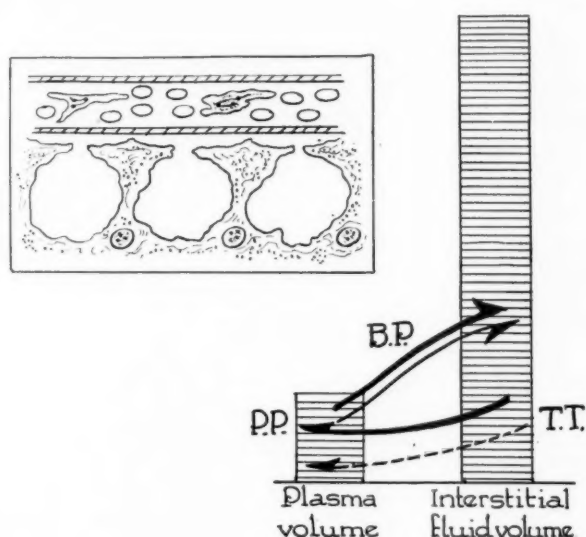


FIG. 5.—Diagrammatic representation of forces affecting P. V.: I. F. V. ratio in chronic sepsis (anemia of weight loss).

B. P., capillary blood pressure; P. P., osmotic pressure of plasma protein; T. T., tissue tension or pressure.

the study were patients with neoplastic lesions of the rectosigmoid colon, but no data as to weight loss were provided in the clinical protocols. However, the unexpected findings of Collier's group are readily explained within the postulated syndrome of "chronic shock." A similar translocation of intravenously administered fluid was recorded in consequence of depletion of the total circulating hemoglobin and in patients with chronic sepsis by Robertson and Bock.²³ Comparable and unexplained shifts of the extracellular fluid were recorded in consequence of surgical operation and ether anesthesia by Stewart and Rourke.¹⁵

In spite of the many uncertainties, the fact remains that there is much of clinical utility in these considerations. The clinical appraisal of weight loss in terms of protein depletion and reduced blood volume has led to more accurate evaluation of the "poor risk" patient than measurements of the concentration

of hemoglobin and plasma protein alone. Correction of blood volume deficits by blood transfusions has proved to be the most important single factor in the preparation of such patients for surgical treatment and subsequently effective utilization of ingested protein. The concept of "chronic shock" is at least temporarily useful in the routine management of debilitated patients, in the comprehension of apparently conflicting clinical studies and in the formulation of new investigative programs of clinically pertinent problems.

CONCLUSIONS

1. Weight loss, decreased blood volume, decreased blood proteins and increased interstitial fluid volume have been correlated as the surgically significant features of protein depletion of the body in a syndrome of "chronic shock."
2. Body protein has been presented as a factor in the dynamic equilibrium of fluid exchange across the capillary wall.
3. The necessity for adoption of some modification of current concepts has been indicated.

REFERENCES

- ¹ Chang, H. C.: Plasma Protein and Blood Volume. *Proc. Soc. Exper. Biol. & Med.*, **29**, 829-832, 1932.
- ² Holman, R. L., Mahoney, E. B., and Whipple, G. H.: Blood Plasma Protein Regeneration Controlled by Diet; Liver and Casein as Potent Diet Factors. *J. Exper. Med.*, **59**, 251-267, 1934.
- ³ Elman, Robert, and Davey, H. W.: Studies on Hypoalbuminemia Produced by Protein-deficient Diets: The Correction of Hypoalbuminemia in Dogs by Means of Large Plasma Transfusions. *J. Exper. Med.*, **77**, 1-5, January, 1943.
- ⁴ Gregersen, M. I.: A Practical Method for the Determination of Blood Volume with the Dye T-1824. *J. Lab. & Clin. Med.*, **29**, 1266-1286, December, 1944.
- ⁵ Varco, R. L.: Preoperative Dietary Management for Surgical Patients: With Special Reference to Lesions of the Stomach and Duodenum. *Surgery*, **19**, 303-378, 1946.
- ⁶ Lyons, Champ: Penicillin Therapy of Surgical Infections in the U. S. Army: A Report. *J. A. M. A.*, **123**, 1007-1018, December 18, 1943.
- ⁷ Starling, E. H.: *The Fluids of the Body*. London, Constable and Co., Ltd. 1909.
- ⁸ Schade, H.: Über Quellungsphysiologie und Ödementstehung, *Ergebn. d. inn. Med. u. Kinderh.*, **32**, 425-463, 1927.
- ⁹ Landerer, A. S.: *Die Gewebsspannung in ihrem Einfluss auf die oertliche Blut- und Lymphbewegung*, Leipzig, 1884.
- ¹⁰ Peters, J. P.: *Body Water. The Exchange of Fluid in Man*. Springfield, Charles C. Thomas, 1935.
- ¹¹ Youmans, J. B., Wells, H. S., Donley, D., and Miller, D. G.: Effect of Posture (Standing) on Serum Protein Concentration and Colloid Osmotic Pressure of Blood from Foot in Relation to Formation of Edema. *J. Clin. Investigation*, **13**, 447-459, 1934.
- ¹² Fulton, J. F.: *Howell's Textbook of Physiology*, Philadelphia. W. B. Saunders Co., 1946.
- ¹³ Gamble, J. L.: *Chemical Anatomy, Physiology and Pathology of Extracellular Fluid*, (a Lecture Syllabus), Harvard Medical School, Boston, Spaulding-Moss, 1941.
- ¹⁴ Warren, J. V., Merrill, A. J., and Stead, E. A., Jr.: *The Role of Extracellular Fluid*

CHRONIC SHOCK

- in the Maintenance of a Normal Plasma Volume. *J. Clin. Investigation*, **22**, 635-641, September, 1943.
- ¹⁵ Stewart, J. D., and Rourke, M.: Changes in Blood Volume and Interstitial Fluid Resulting from Surgical Operations and Ether Anesthesia. *J. Clin. Investigation*, **17**, 413-416, July, 1938.
- ¹⁶ Warren, J. V., and Stead, E. A., Jr.: Fluid Dynamics in Chronic Congestive Heart Failure. *Arch. Int. Med.*, **73**, 138-147, February, 1944.
- ¹⁷ Gibson, J. G., Jr., and Kopp, I.: Studies in the Physiology of Artificial Fever: I—Changes in the Blood Volume and Water Balance. *J. Clin. Investigation*, **17**, 219-232, May, 1938.
- ¹⁸ Weech, A. A., Snelling, C. E., and Goettsch, E.: The Relation between Plasma Protein Content, Plasma Specific Gravity and Edema in Dogs Maintained on a Protein-Inadequate Diet and in Dogs Rendered Edematous by Plasmapheresis. *J. Clin. Investigation*, **12**, 193-216, 1933.
- ¹⁹ Keys, A., Taylor, H. L., Mickelsen, O., and Henschel, A.: Famine Edema and the Mechanism of Its Formation. *Science*, **103**, 669-670, May 31, 1946.
- ²⁰ Gregersen, M. I., Gibson, J. J., and Stead, E. A.: Plasma Volume Determination with Dyes: Errors in Colorimetry; the Use of the Blue Dye T-1824. *Am. J. Physiol.*, **113**, 54-5, September, 1935.
- ²¹ Crandall, L. A., and Anderson, M. X.: Estimation of the State of Hydration of the Body by the Amount of Water Available for the Solution of Sodium Thiocyanate. *Am. J. Digest. Dis.*, **1**, 126-131, April, 1934.
- ²² Schoenheimer, R.: *The Dynamic State of Body Constituents*. Cambridge, Mass., Harvard University Press, 1942.
- ²³ Robertson, O. H., and Bock, A. V.: Blood Volume in Wounded Soldiers. *J. Exper. Med.*, **29**, 139-172, February, 1919.
- ²⁴ Landis, E. M.: Micro-injection Studies of Capillary Permeability: III. The Effect of Oxygen Lack on the Permeability of the Capillary Wall to Fluid and to Plasma Proteins. *Am. J. Physiol.*, **83**, 528-542, January, 1928.
- ²⁵ Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of the Blood Volume: I. Clinical Application of a Method Employing the Azo dye "Evans Blue" and the Spectrophotometer. *J. Clin. Investigation*, **16**, 301-316, May, 1937; II. The Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in 90 Normal Humans. *J. Clin. Investigation*, **16**, 317-328, May, 1937.
- ²⁶ Cruickshank, E. W. H., and Whitfield, I. C.: The Behavior of T-1824 (Evans Blue) in Circulating Blood and a Modified Method for the Estimation of Plasma Volume. *J. Physiol.*, **104**, 52-59, 1945.
- ²⁷ Griffin, G. E., Abbott, W. E., Pride, M. P., Muntwyler, E., Mantz, F. R., and Griffith, L.: Plasma Volume, "Available (Thiocyanate) Volume" and Total Circulating Plasma Protein in Normal Adults. *ANNALS OF SURGERY*, **121**, 352-360, March, 1945.
- ²⁸ Cartwright, G. E., Lauritsen, M. A., Jones, P. J., Merrill, I. M., and Wintrobe, M. M.: The Anemia of Infection: I. Hypoferremia, Hypercupremia and Alterations in Porphyrin Metabolism in Patients. *J. Clin. Investigation*, **25**, 65-80, January, 1946.
- ²⁹ Marriott, W. McK.: Anhydremia. *Physiol. Rev.*, **3**, 275-294, April, 1923.
- ³⁰ Peters, J. P., Wakeman, A. M., and Eisenman, A. J.: The Plasma Proteins in Relation to Blood Hydration: III. The Plasma Proteins in Malnutrition. *J. Clin. Investigation*, **3**, 491-495, February, 1927.
- ³¹ McIver, M. A., and Gamble, J. L.: Body Fluid Changes Due to Upper Intestinal Obstruction. *J. A. M. A.*, **91**, 1589-1592, November 24, 1928.
- ³² Coller, F. A., Iob, V., Vaughan, H. H., Kalder, N. B., and Moyer, C. A.: Translocation of Fluid Produced by the Intravenous Administration of Isotonic Salt Solutions in Man Postoperatively. *ANNALS OF SURGERY*, **122**, 663-677, October, 1945.

(Continue with Part II)

PART II—HEMOGLOBIN AND RED BLOOD CELL DEFICITS
IN CHRONIC SHOCK*

There is good reason to believe that a deficiency of hemoglobin is a factor of primary importance in the problems engendered by depletion of body proteins. Certainly, the wounds of the anemic patient heal slowly and convalescence is generally retarded. A more succinct expression of this general clinical principle has been provided in the experimental work of Whipple, and his coworkers. In the presence of a deficiency of both hemoglobin and tissue protein, priority is assigned to the fabrication of new hemoglobin.^{1, 2} It appears that restoration of protein deficits may be expedited by initial correction of anemia.

There is a definite ceiling on the rate of synthesis of new hemoglobin.^{3, 4} The time required for red blood cell and hemoglobin regeneration may fail to meet the surgical exigency in a chronically ill patient. In many cases operation cannot be wisely postponed until the patient has synthesized adequate quantities of both hemoglobin and tissue protein. Tissue protein regeneration, in the absence of anemia, is accomplished rapidly.⁵ Thus, immediate correction of anemia by whole blood transfusion theoretically assures the deviation of newly available protein to the more rapidly accomplished synthesis of tissue and plasma proteins.

In chronically ill patients the anemia may be so masked by reduction in plasma volume that the hematocrit concentration fails to give a true picture of the existing deficiencies in hemoglobin and red blood cells. Initial observations of surgically significant reductions in blood volume associated with weight loss were made in soldiers with persistently unhealed and suppurative wounds.⁶ Diminished blood volume in debilitated patients has also been noted by Gregersen,⁷ and Varco.⁸ To designate the syndrome characterized by protein depletion, diminished blood volume, and increased susceptibility to shock correctable by transfusion replacement of the blood volume deficit, we⁹ have recently introduced the term, "chronic shock." It is the purpose of this paper to consider the quantitative aspects of the red blood cell and hemoglobin deficits in chronic shock and the correction of these deficits by whole blood replacement.

PROCEDURE AND METHODS

Initial determinations of body weight, plasma volume, hematocrit, hemoglobin concentration and plasma specific gravity were made in 89 patients with a clinical history of weight loss. Included were 41 patients with malignant disease, 28 with chronic infection, eight with hepatic disease, seven with malnutrition and five with peptic ulceration. Among the 89 patients, serially

* This is the second report of a series of studies being conducted under a grant from the Research and Development Division, Office of the Surgeon-General, United States Army.

CHRONIC SHOCK

repeated determinations were made on 59 patients. Sixteen normal subjects with repeated observations on nine served as a control group.

The volume changes in response to transfusion therapy were observed in 33 patients. In most, indicated surgical procedures were performed during the period of hospitalization and initial study. Insofar as possible, blood lost during operation was replaced. Subsequent observations during convalescence were made on an ambulatory program through out-patient facilities. Especial attention was given to a high dietary intake of protein, supplemented when necessary by oral or jejunal feedings of protein digests or hydrolysates.

Considerable care was devoted to standardization of the procedures used. All patients were studied under basal conditions. Breakfast was omitted, and the patients rested quietly in the recumbent position for at least ten minutes before the determinations were made. Blood was drawn from an antecubital vein into syringes coated with a thin film of heparin. Total circulating plasma volume was determined by the method of Gregersen,⁷ the Klett-Summerson photo-electric colorimeter being used. Red blood cell volumes were calculated from hematocrit values obtained with Wintrobe tubes. These tubes, as well as the samples used for obtaining plasma, were centrifuged for 30 minutes at 3,000 revolutions a minute. Hematocrit determinations were made on the samples of blood taken before and after injection of the dye. This served as a check on possible shifts during the ten-minute intervening period. Hemoglobin was determined as oxyhemoglobin by the photo-electric colorimetric method of Evelyn,¹⁰ and total circulating hemoglobin was calculated from the total blood volume value. Specific gravity of the plasma was determined by the falling-drop method of Barbour and Hamilton,¹¹ and plasma protein percentage by the formula of Weech, Reeves, and Goettsch.¹²

EXPERIMENTAL OBSERVATIONS

1. *Estimation of the Standard Circulating Blood Volume for Patients with Weight Loss.*—One of the most difficult problems in the clinical application of blood volume studies is evaluation of an isolated determination in a given patient. Various tables have been compiled to give standard or usual values on the basis of such factors as weight, height, age and sex. Rowntree, Brown and Roth,¹³ and Gibson and Evans,¹⁴ concluded that the blood volume bears a more constant relationship to body surface area than to weight, but their average values on the basis of weight were consistent in people of usual physical configuration. Average values for obese, tall and thin or elderly persons were predicted more accurately by correlation with body surface area. Gregersen, on the other hand, concluded that the correlation of blood volume with weight is as accurate as with body surface area. Particularly significant in this connection are the observations of Courtice¹⁵ on the identity of values based on weight for animals of such different surface areas as the rabbit, dog, goat and horse.

In Table I are presented the results of our determinations in 16 normal subjects as compared to the values reported by previous investigators.^{7, 14-19}

Our average value for plasma volume, 45.5 Ml./Kg. , is practically identical with that reported by Gregersen,⁷ and Stewart and Warren,¹⁹ with the blue dye, T-1824. The average value for total blood volume, 82 Ml./Kg. , is also similar to Gregersen's value of 85 Ml./Kg. Serial determinations in four

TABLE I
COMPARISON OF STANDARD VALUES

Determinations by:	Number of Cases	Method Dye Technic	Plasma Ml./Kg.	Blood Volume Ml./Kg.
Keith, Rowntree, and Geraghty, 1915.....	42	Vital Red	50	85
Bock, 1921.....	5	Vital Red	51	81
Rowntree, Brown, and Roth, 1929.....	78	Vital Red	53	88
Gibson and Evans, 1937.....	49 males 41 females	T-1824	43 males 42 females	78 66
Davis, 1942.....	11	T-1824	40.5	77
Gregersen, 1944.....	51?	T-1824	45	85
Stewart and Warren, 1945.....	29	T-1824	45	..
Present series, 1946.....	16	T-1824	45.5	82

TABLE II
RELATIONSHIP OF BLOOD VALUES TO OBSERVED AND USUAL WEIGHT

Case No. and Diagnosis	Weight Observed and Usual	Total Hemoglobin	Total Cell Volume	Total Blood Volume
		Percentage of Standard for Weight*		
Case 306..... Carcinoma of stomach 83% of usual weight	Observed 48.1 Kg.	61	65	85
	Usual 58 Kg.	49	52	70
Case 301..... Carcinoma of colon 89% of usual weight	Observed 50.3 Kg.	69	67	100
	Usual 81.2 Kg.	41	41	60
Case 308..... Carcinoma of pancreas 62% of usual weight	Observed 43.5 Kg.	77	88	102
	Usual 69.8 Kg.	49	54	62
Case 403..... Achalasia 63% of usual weight	Observed 31.7 Kg.	81	93	131
	Usual 53.3 Kg.	54	58	84

* Standard values are taken from Gregersen.⁷

Total hemoglobin = 12.75 Gm./Kg. ; total red cells = 40 Ml./Kg. ; blood volume = 85 Ml./Kg.

normal subjects at varying intervals over a period of seven months showed a remarkable constancy, the range of variation being within 10 per cent.⁹

The data given in Table I suggest a close relationship between blood volume and body weight and indicate that standard values for the blood volume

CHRONIC SHOCK

of the normal individual can be safely calculated from observed weight. Table II indicates, however, that the problem is more complex when patients with progressive weight loss are involved. In transfusing such patients, one is confronted with the problem of selecting a standard on the basis of the optimal weight in health or on the basis of the observed weight in illness. Thus, in the four representative cases shown in Table II, it is seen that malnourished patients may have total hemoglobin, red cell and total blood volume values near

TABLE III
EFFECTS OF REPLACEMENT THERAPY

Case No., Diagnosis and Treatment	Determinations	Total Hemoglobin	Total Cell Volume	Blood Volume
		Percentage of Standard for Weight		
Case 306—64-year-old male..... Carcinoma of stomach Usual weight 128 lbs. (48.1 Kg.) Radical resection 4/26/'46 Procedure well tolerated Uneventful convalescence	4/10/'46			
	Weight 83% of usual	49	42	70
	4/26/'46—following replacement therapy with 3,000 Ml. Weight 78% of usual	100	115	106
	5/9/'46			
	3 weeks postoperative Weight 65% of usual	83	90	89
	6/20/'46			
Case 326—57-year-old male. Esophageal stricture Following esophagogastrrectomy for malignancy (March, 1946) Usual weight 220 lbs. (99.8 Kg.) Gastrostomy 7/5/'46 Rapid clinical recovery following dilatation	Postoperative Weight 66% of usual	89	93	94
	7/1/'46			
	Weight 68% of usual	56	65	73
	7/5/'46—following replacement with 2,500 Ml. Weight unchanged	113	118	126
	7/17/'46			
	High protein gastrostomy feeding. Weight unchanged	90	90	78
	8/27/'46			
	Able to swallow high protein diet Weight 73% of usual	100	102	98

the assumed standard for their observed weight. Values calculated on the basis of their usual weight, however, are significantly lower. It may finally be pointed out that when blood volume for a patient with weight loss is computed on each of the three bases commonly used; that is, weight, surface area and height, better agreement is reached between the values based on weight and those obtained by the other methods if the normal, rather than the observed weight, is used. From inspection of the Dubois formula ($A = W^{0.425} \times H^{0.725} \times C$) for surface area it is seen that a given loss in weight is accompanied by a smaller relative loss in surface area. Thus, a 25 per cent weight loss by

a 71-inch man who formerly weighed 186 lb. is attended by a 13 per cent decrease in surface area.

In similar patients one of us⁶ found it clinically practicable to restore the blood volume by transfusion to the standard value for the patient's usual weight without evidence of significant hemoconcentration or overloading of the vascular reservoir. The significance of this observation has been questioned on the basis of inadequate studies during convalescence to indicate maintenance of the blood volume at this higher level.²⁰ Table III shows the results of two typical experiments indicating that during convalescence after transfusion and appropriate surgical treatment the values for total circulating hemoglobin and total red blood cell mass are maintained at, or near, the standard value for the patient's usual weight in health. It is significant that restoration of

TABLE IV
STANDARD VALUES IN OBESE AND IN TALL AND THIN PATIENTS, AND IN PROTRACTED ILLNESS

Case No. and Diagnosis	Body Type	Weight Usual and Standard	Plasma Volume	Blood Volume
			Percentage of Standard	
Case 427..... Duodenal and esophageal ulceration (2,000 ML. of blood prior to determinations)	Obese prior to illness	Usual weight 88.9 Kg.	82	72
		Standard for age, sex and height 68 Kg.	100	93
Case 520..... Bronchiectasis	Tall and thin	Usual weight 61.7 Kg.	104	99
		Standard for age, sex and height 79.4 Kg.	83	84
Case 518..... Bronchiectasis	Ill since childhood— never attained optimal weight	Usual weight 39.9 Kg.	100	89
		Standard for age, sex and height 50.8 Kg.	80	72

blood volume during convalescence precedes significant gain in weight. This is strikingly illustrated in Case 326 in which the transfusion of 2,500 ML. of blood elevated the hemoglobin, red cell and blood volumes well above standard levels based on his usual weight. Following correction of an esophageal stricture and adequate dietary intake, these levels were maintained for six weeks with only a slight increase in weight.

We have found that in approximately 5 per cent of the cases the calculations of standard values on the basis of usual weight in health are not applicable. This is true in instances of excessive obesity prior to illness, in tall and thin patients and in protracted illness wherein optimal weight had never been attained. Our data (Table IV) suggest that in such cases it is preferable to use values based on standard weight tables for sex, age and height. It has not been found necessary to correct standards for the older age groups.

Further factual evidence supporting the use of standards based on usual weight in health is presented in Table V. Restoration of the blood volume

CHRONIC SHOCK

to the standard volume assigned on the basis of the usual weight in health may give values up to 150 per cent of normal for the observed weight. This has been accomplished without clinical or laboratory evidence of overloading of the vascular reservoir.

TABLE V
RESULTS OF TRANSFUSION THERAPY

Case No. and Diagnosis	Ml. of Blood Given	Hemato- crit %	Weight Observed and Usual	Total Hemoglobin	Total Cell Volume	Blood Volume
				Percentage of Standard		
Case 403..... Achalasia 63% of usual weight, 50.3 Kg.	1,500	40	Observed	120	123	144
			Usual	93	88	105
Case 327..... Carcinoma of lung 82% of usual weight, 61.7 Kg.	2,000	45	Observed	129	133	118
			Usual	113	119	105
Case 308..... Carcinoma of pancreas 62% of usual weight, 69.6 Kg.	2,000	49	Observed	102	114	110
			Usual	65	71	68
Case 322..... Carcinoma of lung 86% of usual weight, 103 Kg.	3,000	50	Observed	123	128	120
			Usual	103	108	103
Case 338..... Carcinoma of esophagus 83% of usual weight, 77 Kg.	2,350	52	Observed	124	132	120
			Usual	104	109	97
Case 306..... Carcinoma of stomach 83% of usual weight, 58 Kg.	3,000	53	Observed	127	135	136
			Usual	100	115	106
Case 332..... Carcinoma of pancreas 83% of usual weight, 73.8 Kg.	2,000	54	Observed	122	126	111
			Usual	101	107	91
Case 302..... Carcinoma of esophagus 87% of usual weight, 71.7 Kg.	3,500	54	Observed	122	133	119
			Usual	100	114	99
Case 334..... Carcinoma of lung 81% of usual weight, 68 Kg.	2,500	54	Observed	131	129	117
			Usual	108	110	96
Case 326..... Stricture of esophagus 89% of usual weight, 99.8 Kg.	2,500	55	Observed	168	175	150
			Usual	113	118	126

2. *Determination of Blood Volume in Patients with Weight Loss Due to Various Causes.*—Reduced blood volume was observed in all cases of weight loss investigated. In Table VI it is shown that average blood volumes for the various groups, expressed as per cent of standard for usual weight, were as follows: Malignancy, 72 per cent; chronic infection, 76 per cent; hepatic disease, 67 per cent; malnutrition, 76 per cent; and peptic ulceration, 79 per cent. The deficit is approximately one-fourth the value accepted as standard for the patient in health. The reduction in total hemoglobin and red cell mass

is more pronounced than that in total blood volume. The average total hemoglobin ranged from 50 to 66 per cent of the standard and the average total red blood cell mass ranged from 56-70 per cent of the standard. It is obvious that in this group of cases a clinical history of weight loss has consistently indicated reduction in blood volume and total circulating red cell mass.

3. *Total Circulating Hemoglobin and Total Red Cell Mass in Estimating Replacement Needs.*—Studies in World War II confirmed the existence of reduced blood volume in consequence of traumatic injuries.^{19, 21-25} In such

TABLE VI
TABULATION OF DEFICITS ASSOCIATED WITH WEIGHT LOSS

Disease	No. of Cases	Weight	Total Hemoglobin Per Cent of Standard	Total Cell Volume Per Cent of Standard	Plasma Volume Per Cent of Standard	Blood Volume
Malignancy.....	41	83	50	58	84	72
Chronic infection.....	28	87	59	59	92	76
Hepatic disease.....	8	84	52	56	84	67
Malnutrition.....	7	78	53	61	91	76
Peptic ulceration.....	5	85	66	70	88	79

TABLE VII
CORRELATION BETWEEN ANEMIA AND DIMINISHED PLASMA PROTEIN CONCENTRATION
IN TRAUMATIC INJURIES*

Hematocrit	Plasma Protein in G. %						Total Patients
	5.6-6	6.6-6.5	6.6-7	7.1-7.5	7.6-8	8.1-8.5	
20-30.....	2	9	4				15
31-40.....	2	6	14	14	3		39
41-50.....		6	8	19	4	1	38
Total patients..	4	21	26	33	7	1	92

* These observations were made in collaboration between Major Jos. E. Edwards and one of us (C. L.), by the CuSO₄ method, April, 1944.

injuries, there was correlation between anemia and plasma protein concentration (Table VII). Base Hospital surgeons, concerned with correction of anemia prior to reparative surgery and during early convalescence, evolved a rough "rule-of-thumb" to estimate transfusion requirements. It was recommended²⁶ that 500 ML. of whole blood be given for each three-point deficit in the hematocrit. In practice, it was found safe to give 1,000 ML. daily when the hematocrit was below 40 per cent, and 500 ML. daily for a hematocrit of 40 to 45 per cent. In chronic shock, however, dosages based on hematocrit deficits are of little value because of the reduced plasma volume. The hematocrit concentration does not give a true picture of the existing deficiencies. Adequate restoration can be accomplished only by restoration of the total circulating hemoglobin or red cell mass, but the deficits cannot be determined accurately without blood volume studies.

As a result of our experience, certain general conclusions as to the amount of blood usually required may be drawn. The average hemoglobin deficit was 415 Gm. and the average deficit in red cell volume was 1,200 ML. On the assumption that each 500 ML. of transfused blood contains 75 Gm. of hemo-

CHRONIC SHOCK

globin and 225 Ml. of red blood cells, the average dosage of blood required was 2,700 Ml. In no instance has less than 1,500 Ml. been given and in some patients 4,000 Ml. has been necessary.

By definition, correction of anemia implies restoration of total hemoglobin to standard value. This has been attended by definite but asymptomatic

TABLE VIII
RESULTS OF REPLACEMENT THERAPY

Case No. and Diagnosis	Transfusion Therapy*	Total Hemoglobin	Total Cell Volume
		Percentage of Standard	
(A) In absence of continued bleeding			
Case 335—Carcinoma of lung.	Prior to transfusion	65	72
Estimated transfusion dosage 1,800 Ml.			
Usual weight 79.8 Kg.	After transfusion with 2,000 Ml.	110	112
Case 334—Carcinoma of lung.	Prior to transfusion	58	63
Estimated transfusion dosage 2,300 Ml.			
Usual weight 68 Kg.	After transfusion with 2,500 Ml.	108	110
Case 509—Chronic empyema.	Prior to transfusion	56	57
Infection controlled with penicillin			
Estimated transfusion dosage 2,000 Ml.	After transfusion with 2,000 Ml.	103	115
Usual weight 47.6 Kg.			
Case 522—Bronchiectasis.	Prior to transfusion	67	66
Estimated transfusion dosage 1,650 Ml.			
Usual weight 61.2 Kg.	After transfusion with 1,500 Ml.	92	102
(B) In presence of continued bleeding			
Case 428—Large gastric ulcer.	Prior to transfusion	62	60
Estimated transfusion dosage 2,000 Ml.			
Usual weight 62.6 Kg.	After transfusion with 2,000 Ml.	65	64
Case 312—Large carcinoma of stomach. . . .	Prior to transfusion	56	59
Estimated transfusion dosage 3,200 Ml.			
Usual weight 86 Kg.	After transfusion with 3,000 Ml.	80	81
Case 324—Carcinoma of head of pancreas, with common duct obstruction	Prior to transfusion	66	73
Estimated transfusion dosage 2,000 Ml.			
Usual weight 70 Kg.	After transfusion with 3,350 Ml.	88	81

* The transfusion dosage was based on deficit in total grams of hemoglobin.

hemoconcentration. On the other hand, restoration of total circulating red cell volume has given clinically satisfactory results and more nearly normal hematocrit values.

No untoward complications have been attributable to mild hemoconcentration. In the absence of quantitative blood volume determinations, correction of the masked anemia in chronic shock may be attained by transfusion toward this goal. As demonstrated in Table V, a hematocrit of 50 per cent has consistently indicated restoration of blood volume values to the standard level.

4. *Quantitative Aspects of Transfusion Therapy in Blood Volume Replacement.*—In Table VIII it is shown that in a given case transfusion to replace the estimated deficit may, or may not, restore the blood volume. The first half of the table (VIII-A) records quantitative replacements in patients

with lesions which did not bleed. No evidence of the replenishment of "body storehouses" of hemoglobin, as suggested by Stewart and Warren,¹⁹ was observed. In the latter half of the table (VIII-B) are included patients with protracted gastro-intestinal bleeding and incomplete correction of the blood volume deficit on the basis of quantitative therapy. In Case 324, nearly twice the estimated dosage was necessary. We are in agreement with Emerson and Ebert²¹

TABLE IX
RESULTS OF TRANSFUSION THERAPY IN CHRONIC SHOCK

Case No. and Diagnosis	Transfusion Therapy	Total Cell Volume	Plasma Volume	Blood Volume
		Percentage of Standard		
Case 326.	Before	38	48	44
Carcinoma of esophagus				
Usual weight 99.8 Kg.	After	114	86	99
Case 306.	Before	52	85	70
Carcinoma of stomach				
Usual weight 58 Kg.	After	115	94	106
Case 338.	Before	57	77	68
Carcinoma of esophagus				
Usual weight 77 Kg.	After	109	86	97
Case 322.	Before	54	77	65
Carcinoma of lung				
Usual weight 103 Kg.	After	108	100	103
Case 335.	Before	72	83	79
Carcinoma of lung				
Usual weight 79.8 Kg.	After	112	98	104
Case 482.	Before	45	69	56
Hepatic disease				
Usual weight 68 Kg.	After	109	102	103
Case 480.	Before	30	95	63
Hepatic disease				
Usual weight 91.6 Kg.	After	91	118	103
Case 481.	Before	60	66	63
Hepatic disease				
Usual weight 79.4 Kg.	After	95	77	85

that failure of quantitative replacement is a consequence of continued blood loss. It is clinically important to identify these cases for more intensive transfusion therapy followed promptly by corrective surgical procedures.

In chronic shock the plasma volume may be persistently increased following transfusion therapy (Table IX). The observed increase approximates but rarely equals, or exceeds, the gain in red cell volume. It is felt that this observation further supports the concept of a reduced blood volume in chronic shock. A persistent increase in plasma volume after transfusion is at variance with previous observations. It has been generally accepted²⁷⁻²⁹ that blood volume increases two or three days after transfusion are due solely to augmented cell mass because of compensatory return of plasma volume to the pretransfusion level. After transfusion therapy in chronic shock, the increase in plasma volume has been demonstrated to persist for several months.

5. *Tolerance for Surgical Procedures in Patients with Restored Blood Volume.*—Figure 6 illustrates a representative anesthetic record of a properly prepared patient in chronic shock (Patient 306, Table III). This was a 64-year-old man with carcinoma of the stomach, whose initial total hemoglobin and red blood cell volume were approximately 50 per cent of standard for usual weight. Preoperative transfusion of 3,000 Ml. of blood restored the values to standard levels. He underwent a four-hour operative procedure which included gastrectomy, subtotal pancreatectomy, splenectomy, resection of greater omentum, colostomy, and jejunostomy. Three whole blood transfusions of 500 Ml. each were given to replace the blood lost during operation. In spite of this extensive procedure the systolic blood pressure did not vary by

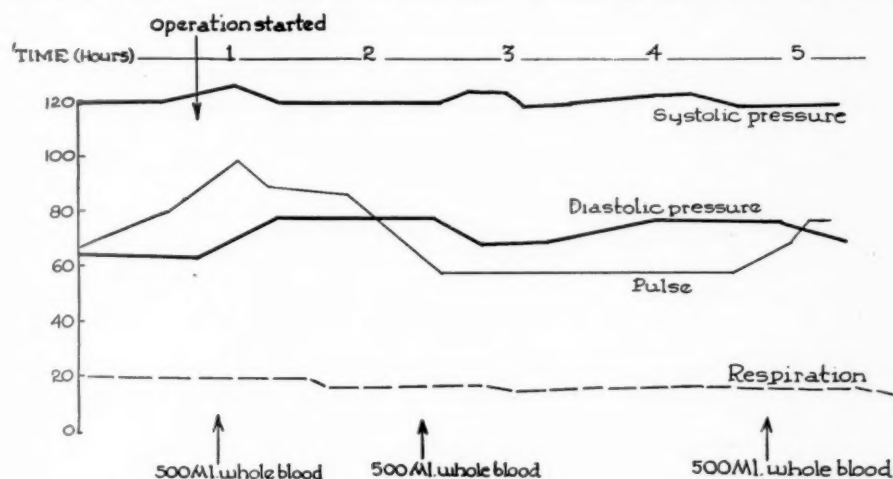


FIG. 6.—Anesthetic record of Case 306. Cyclopropane and ether, endotracheal technic. See text for details.

more than 10 mm. mercury throughout the operative period, and the diastolic pressure remained at, or above, the preoperative level. Pulse rate and respiration also showed minimal fluctuations.

The poor tolerance of the inadequately prepared depleted patient for blood loss during necessary surgical procedures is generally recognized. Abbott,³⁰ and Meyer,³¹ have recommended empirically that blood transfusions be given preoperatively to all patients with peptic ulceration or carcinoma of the colon, even in the absence of anemia. They have attributed to dehydration the nearly normal hemoglobin and hematocrit concentrations observed in these patients. Such a concept of dehydration seems inadequate to explain the established need for blood transfusion in the preoperative preparation of depleted patients.

We have presented evidence that a reduction in blood volume is part of the surgically significant pattern of protein depletion. The significance of the reduced effective blood volume in the patient with weight loss is supported by the unquestionably increased tolerance of the adequately transfused "poor

risk" patient for major surgical procedures. It is further supported by the demonstration of a maintained increase in blood volume prior to significant weight gain during convalescence.

It is doubtful that total restoration of the standard circulating hemoglobin or red blood cell volume is necessary for satisfactory wound healing and convalescence. The critical level of total hemoglobin for optimal synthesis of tissue and plasma protein remains to be evaluated.

SUMMARY AND CONCLUSIONS

1. Reduction in blood volume is part of the surgically significant pattern of protein depletion.
2. Blood volume deficits in depleted patients should be calculated on the basis of standard for usual weight prior to illness.
3. Correction of hemoglobin or red cell deficits by repeated blood transfusion restores the volume to the standard value without producing clinically significant hemoconcentration.
4. During convalescence associated with recovery from disease there is evidence of maintained reestablishment of the blood volume.
5. In the absence of continued bleeding, blood volume replacement by transfusion therapy is quantitative.
6. Quantitative correction of blood volume deficits by whole blood transfusions increases the tolerance of the "poor risk" patients for major surgical procedures.

BIBLIOGRAPHY

- 1 Whipple, G. H., and Madden, S. C.: Hemoglobin Plasma Protein and Cell Protein: Their Interchange and Construction in Emergencies. *Medicine*, **23**, 215-224, September, 1944.
- 2 Madden, S. C., Kattus, A. A. Jr., Carter, J. R., Miller, L. L., and Whipple, G. H.: Plasma Protein Production as Influenced by Parenteral Protein Digests: Very High Protein Feeding and Red Blood Cell Catabolism. *J. Exper. Med.*, **82**, 181-191, September, 1945.
- 3 Fowler, W. M., and Barer, A. P.: Rate of Hemoglobin Regeneration in Blood Donors. *J. A. M. A.*, **118**, 420-427, February 7, 1942.
- 4 Alstead, Stanley: Rate of Blood-regeneration after Hemorrhagia, *Lancet*, **1**, 424-426, April 3, 1943.
- 5 Co Tui, Bartter, F. C., Wright, A. W., and Holt, R. B.: Red Cell Reinfusion and Frequency of Plasma Donations: Preliminary Report of Multiple Donations in Eight Weeks by Each of Six Donors. *J. A. M. A.*, **124**, 331-336, February 5, 1944.
- 6 Lyons, Champ: Penicillin Therapy of Surgical Infections in the U. S. Army: Report. *J. A. M. A.*, **123**, 1007-1018, December 18, 1943.
- 7 Gregersen, M. I.: Practical Method for Determination of Blood Volume with Dye T-1824; Survey of Present Basis of Dye-method and its Clinical Applications. *J. Lab. & Clin. Med.*, **29**, 1266-1286, December, 1944.
- 8 Varco, R. L.: Preoperative Dietary Management for Surgical Patients. *Surgery*, **19**, 303-378, March, 1946.
- 9 Lyons, Champ, Mayersen, H. S., Clark, J. H., Nelson, W., and DeCamp, P.: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient: I—Concept of Chronic Shock, (in press).
- 10 Evelyn, K. A.: Stabilized Photoelectric Colorimeter with Light Filters. *J. Biol. Chem.*, **115**, 63-75, August, 1936.

- 11 Barbour, H. G., and Hamilton, W. F.: The Falling-drop Method for Determining Specific Gravity. *J. Biol. Chem.*, **69**, 625-640, August, 1926.
- 12 Weech, A. A., Reeves, E. B., and Goettsch, E.: The Relationship between Specific Gravity and Protein Content in Plasma, Serum and Transudate from Dogs. *J. Biol. Chem.*, **113**, 167-174, February, 1936.
- 13 Rowntree, L. G., Brown, G. E., and Roth, G. M.: The Volume of the Blood and Plasma in Health and Disease. Philadelphia, W. B. Saunders Company, 1929.
- 14 Gibson, J. G., Jr., and Evans, W. A., Jr.: Clinical Studies of Blood Volume II: Relation of Plasma and Total Blood Volume to Venous Pressure, Blood Velocity Rate, Physical Measurements, Age and Sex in 90 Normal Humans. *J. Clin. Investigation*, **16**, 317-328, May, 1937.
- 15 Courtice, F. C.: Blood Volume of Normal Animals. *J. Physiol.*, **102**, 290-305, December 31, 1943.
- 16 Keith, N. M., Rowntree, L. G., and Geraghty, J. T.: A Method for the Determination of Plasma and Blood Volume. *Arch. Int. Med.*, **16**, 547-576, October, 1915.
- 17 Bock, A. V.: The Constancy of the Volume of Blood Plasma. *Arch. Int. Med.*, **27**, 83, January, 1921.
- 18 Davis, L. J.: The Determination of the Blood Volume in Man with Evans Blue ("T-1824"). *Edinburgh Med. J.*, **49**, 465-483, August, 1942.
- 19 Stewart, John D., and Warren, Frank: Observations on Severely Wounded in Forward Field Hospitals: With Special Reference to Wound Shock. *ANNALS OF SURGERY*, **122**, 129-147, August, 1945.
- 20 Cartwright, G. E., Lauritsen, M. A., Jones, P. J., Merrill, I. M., and Wintrobe, M. M.: The Anemia of Infection: I. Hypoferremia, Hypercupremia, and Alterations in Porphyrin Metabolism in Patients. *J. Clin. Investigation*, **25**, 65-80, January, 1946.
- 21 Emerson, C. P., and Ebert, R. V.: Reduced Blood Volume: A Study of Shock in Battle Casualties. *ANNALS OF SURGERY*, **122**, 745-772, November, 1943.
- 22 Gregersen, M. I.: Traumatic Shock. *Bull. New York Acad. Med.*, **19**, 666, September, 1943.
- 23 Cournand, A., *et al.*: Studies of Circulation in Clinical Shock. *Surgery*, **13**, 964-995, June, 1943.
- 24 Richards, D. W., Jr.: Circulation in Traumatic Shock in Man. (Harvey Lecture, February 17, 1944), *Bull. New York Acad. Med.*, **20**, 363-393, July, 1944.
- 25 Noble, R. P., and Gregersen, M. I.: Blood Volume in Clinical Shock. I—Mixing Time and Disappearance Rate of T-1824 in Normal Subjects and in Patients in Shock: Determination of Plasma Volume in Man from 10-minute Sample. *J. Clin. Investigation*, **25**, 158-171, March, 1946.
- 26 Office of the Surgeon-General, Surgical Consultants Division: Blood Transfusion in the Reparative Management of Battle Wounds. *Bull. U. S. Army Med. Dept.*, **85**, 4-5, February, 1945.
- 27 Boycott, A. E., and Oakley, C. L.: Adjustment of Blood Volume after Transfusion. *J. Path. & Bact.*, **38**, 91-97, January, 1934.
- 28 Sibley, W. L., and Lundy, J. S.: Blood Volume and Hemoglobin after Transfusion. *Surg., Gynec. & Obst.*, **67**, 490-494, October, 1938.
- 29 Kilduffe, R. A., and DeBakey, Michael: The Blood Bank and the Technique and Therapeutics of Transfusions. St. Louis, C. V. Mosby Co., 1942.
- 30 Abbott, W. E., and Mellors, R. C.: Total Circulating Plasma Proteins in Surgical Patients, with Dehydration and Malnutrition; Indications for Intravenous Alimentation with Amino-acids. *Arch. Surg.*, **46**, 277-288, February, 1943.
- 31 Meyer, K. A., and Kozoll, D. D.: Primary Resection of the Colon: With Special Reference to Surgical Diagnosis and Management. *S. Clin. North America*, **26**, 176-199, February, 1946.

(Continue with Part III)

PART III—QUANTITATIVE ASPECTS OF THE ANEMIA
ASSOCIATED WITH MALIGNANT TUMORS*

Anemia and nutritional depletion are recognized features of neoplastic cachexia. Sachar, and coworkers,¹ and Ariel, and associates,² have emphasized the plasma protein concentration as the best index of reserve body protein. Evans³ has urged determination of the total circulating plasma protein as more informative. It has seemed to us that these considerations of plasma protein as an index of tissue protein reserves neglect the important factor of the other body protein—hemoglobin.^{4, 5} Obviously, it is pertinent to consider the relative deficiencies of both tissue protein and hemoglobin.

Progressive anemia is often more apparent clinically than is the loss of tissue protein in the patient with advancing neoplastic disease. The etiologic factors usually emphasized in the production of this anemia are continued bleeding, interference with nutrition, and metastasis to bone marrow.^{6, 7} There is also good evidence to show that the anemia in malignant disease may result from interference with hemoglobin formation.⁸ Kracke⁹ states that any type of malignancy in any tissue is capable of producing anemia and suggests that the malignant process either elaborates a product capable of bone marrow inhibition or utilizes substances necessary for red cell production. Clark, Power, Heck and Dixon¹⁰ have described a deficiency of iron associated with carcinoma of the proximal portion of the colon. Ewing¹¹ stresses the absorption of hemolytic agents from infected and ulcerating surfaces and from necrosing areas of closed tumors as an important factor. Watson and Young,¹² and Jones and Tillman,¹³ have reported the cure of severe hemolytic anemia following surgical removal of dermoid tumors of the ovary.

Previous studies of the anemia in malignant disease have been primarily concerned with the concentration of red blood cells and hemoglobin.^{10, 14, 15} Ewing,¹¹ however, has stated that most malignant tumors are associated with progressive deterioration in the quality and quantity of the blood. He refers to the work of Louis, in 1846, as showing that the total quantity of the blood is usually much diminished in malignancy. It is the purpose of this report to present observations on the quantity and quality of the circulating blood in patients with malignant disease.

PROCEDURE AND METHODS

Blood volume studies were made under basal conditions in 38 patients hospitalized for treatment of malignant tumors. Serially repeated determinations were made in 23 patients. There were ten patients with carcinoma of the stomach or lower portion of the esophagus, six with carcinoma of the pancreas, four with carcinoma of the colon, and ten with carcinoma of the lung. A miscellaneous group included three patients with sarcoma, two with disseminated carcinomatosis, one with carcinoma of the ureter, one with carcinoma of the breast, and one with widespread mycosis fungoides.

* This is the third report of a series of studies being conducted under a grant from the Research and Development Division, Office of the Surgeon-General, United States Army.

The laboratory determinations were performed in accordance with the technic previously outlined,⁵ the Gregersen method¹⁶ as modified for the Klett-Summerson photo-electric colorimeter being used. Red cell volumes were calculated from hematocrit values obtained after centrifuging heparinized blood for 30 minutes at 3,000 revolutions per minute in Wintrobe tubes. Hemoglobin was determined as oxy-hemoglobin by the photo-electric colorimetric method of Evelyn.¹⁷ Plasma specific gravity was determined by the falling-drop method of Barbour and Hamilton¹⁸ and plasma protein concentration by the formula of Weech, Reeves and Goettsch.¹⁹

The basis for calculation of standard values for the blood volume studies was the patient's usual weight in health.⁵ The diagnosis of malignancy was confirmed in all cases by histologic examination of tissue removed at operation.

EXPERIMENTAL OBSERVATIONS

I. Carcinoma of the Stomach or Lower Portion of the Esophagus: The initial values obtained in ten patients are presented in Table X. The severity of the anemia is graphically illustrated in the averaged alterations from standard (Fig. 7). The red cell mass is markedly reduced, and the cells are deficient in hemoglobin. In contrast to this finding, several of the cases have normal, or nearly normal, total plasma proteins with normal or increased plasma volume. In only one instance (Case 302) was there comparable reduction in total plasma protein and hemoglobin. The high plasma volume recorded is open to variable explanation. Patient 314 had an obstructive lesion of the cardia and had been maintained on high caloric, high protein gastrostomy feedings for three months prior to study. Patient 318 inadvertently received 2,000 Ml. of glucose solution in the 12-hour period prior to study. Patient 325 had concomitant amebiasis and intestinal bleeding. It was impossible to correlate hepatic or other metastases with any pattern of change.

II. Carcinoma of the Pancreas: There were six patients with carcinoma of the head of the pancreas and obstructive jaundice. Two patients (Cases 308 and 332) had primary tumors of the body and tail of the pancreas, with a clinical history of considerable weight loss and progressive anorexia. Both of these latter cases were found to have regional and hepatic metastases at operation. The observations on these six patients are summarized in Table XI. With the exception of one previously transfused patient, there was a deficit of both plasma protein and hemoglobin. In three of the four severely jaundiced patients (Cases 307, 324 and 329), the plasma volume was not significantly reduced from the standard value in spite of considerable weight loss and reduced total plasma protein. In Figure 8 the graphic illustration of the averaged values emphasizes the deficiencies of red cell mass and hemoglobin.

III. Carcinoma of the Colon: The findings in four patients are summarized in Table XII. Patient 316 had multiple hepatic metastases and obstructive jaundice three years after resection. The other patients had early and resectable lesions. The series is too small for separate appraisal, but the averaged

TABLE X
CARCINOMA OF THE STOMACH OR LOWER PORTION OF THE ESOPHAGUS

Case No.	Weight		Hematocrit		Total Circulating Hemoglobin		Total Plasma Protein		Plasma Volume		Red Cell Mass		Blood Volume	
	Observed (Kg.)	Usual (Kg.)	Observed	% of Standard	Observed (Gm.)	% of Standard	Observed (Gm.)	% of Standard	Observed (ML)	% of Standard	Observed (ML)	% of Standard	Observed (ML)	% of Standard
302*	56.7	71.7	41	87	331	36	90	43	1,550	48	1,080	38	2,630	44
304	76.7	82.6	35	74	348	34	182	76	2,985	80	1,605	49	4,510	66
306	48.1	58.1	36	76	369	49	146	86	2,205	85	1,240	52	3,445	70
312*	66.2	86.2	44	94	621	56	162	66	2,540	65	1,995	59	4,530	62
314*	53.1	68	28	59	374	43	192	100	3,360	116	1,305	48	4,668	81
318*	49.9	59	24	57	248	33	147	86	3,025	116	960	40	3,985	80
325*	59	72.6	25	59	267	29	193	92	3,865	118	1,300	40	5,155	84
340	42.6	55.5	37	88	422	61	115	73	2,415	100	1,420	64	3,835	83
338	64.4	77.1	39	83	521	53	195	89	2,692	77	1,721	57	4,413	68
346	42.2	55.3	34	72	373	54	196	125	2,967	123	1,120	51	4,087	88
Average	55.8	68	34	75	387	45	162	83	2,760	93	1,375	50	4,126	73

* Metastases.

TABLE XI
CARCINOMA OF PANCREAS

Case No.	Weight		Hematocrit		Total Circulating Hemoglobin		Plasma Protein		Plasma Volume		Red Cell Mass		Blood Volume	
	Observed (Kg.)	Usual (Kg.)	Observed	% of Standard	Observed (Gm.)	% of Standard	Observed (Gm.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard	Observed (Ml.)	% of Standard
307.....	43.1	65.8	38	81	376	46	145	78	2,340	93	1,430	55	3,770	68
308.....	43.5	69.9	41	87	430	49	132	66	2,190	70	1,521	54	3,710	62
315.....	59	97.5	37	78	484	39	183	65	2,630	61	1,542	39	4,170	50
324.....	62.6	70.3	41	87	584	66	119	59	2,915	92	2,030	73	4,945	83
329*.....	49.4	61.2	39	83	513	65	210	120	2,675	99	1,715	69	4,387	85
332.....	60.3	74.8	45	96	585	62	163	76	2,315	68	1,895	64	4,205	66
Average.....	53	73.3	40	85	495	55	159	77	2,510	80	1,690	59	4,200	69

* 1,000 MI. blood transfused 18 days prior to determination.

CHRONIC SHOCK

TABLE XII
CARCINOMA OF COLON

Case No.	Weight		Hematocrit		Total Circulating Hemoglobin		Plasma Protein		Plasma Volume		Red Cell Mass		Blood Volume	
	Observed (Kg.)	Usual (Kg.)	Observed	% of Standard	Observed (Gm.)	% of Standard	Observed (Gm.)	% of Standard	Observed (ML.)	% of Standard	Observed (ML.)	% of Standard	Observed (ML.)	% of Standard
303.....	54.9	72.6	39	83	524	57	199	90	2,760	86	1,760	62	4,520	75
316*.....	52.2	64.4	36	86	338	42	60	33	1,975	71	1,110	44	3,085	57
321.....	72.6	81.6	40	95	430	42	197	86	2,430	66	1,620	50	4,055	58
341.....	60.3	74.8	36	86	446	47	168	78	2,480	73	1,396	48	3,875	61
Average.....	60	73	38	87.5	435	47	156	72	2,410	74	1,470	51	3,885	63
* Metastases.														

TABLE XIII
CARCINOMA OF THE LUNG

Case No.	Weight		Hematocrit		Total Circulating Hemoglobin		Plasma Protein		Plasma Volume		Red Cell Mass		Blood Volume	
	Observed (Kg.)	Usual (Kg.)	Observed	% of Standard	Observed (Gm.)	% of Standard	Observed (Gm.)	% of Standard	Observed (ML.)	% of Standard	Observed (ML.)	% of Standard	Observed (ML.)	% of Standard
305*.....	57.6	67.9	38	81	451	52	148	74	2,410	80	1,465	53	3,880	68
313*.....	54.4	65.8	37	76	451	55	200	108	2,915	103	1,640	63	4,560	82
322*.....	89.4	103.4	39	83	663	48	234	77	3,490	77	2,230	54	5,715	65
323*.....	55.3	61.2	49	104	756	96	141	80	2,695	100	2,590	105	5,285	102
328.....	65.8	86.2	43	91	849	77	252	103	3,810	100	2,875	81	6,685	91
331*.....	65.8	77.1	43	91	698	70	176	80	2,905	83	2,190	73	5,095	78
333*.....	62.6	68	45	96	729	85	198	100	2,825	97	2,310	85	5,135	90
334*.....	56.7	68	38	81	503	58	136	73	2,785	96	1,710	63	4,490	78
335.....	72.6	79.8	43	91	657	65	187	83	2,995	83	2,260	72	5,255	79
336*.....	63	84.4	38	81	522	47	203	84	2,840	76	1,740	52	4,580	64
Average.....	64	76.2	41	88	628	65	188	86	2,967	89	2,101	70	5,068	80
* Metastases.														

values shown in Figure 9 suggest conformity with other lesions of the gastrointestinal tract.

IV. Carcinoma of the Lung: The determinations on ten patients included in this series are summarized in Table XIII. In five patients (Cases 313, 323,

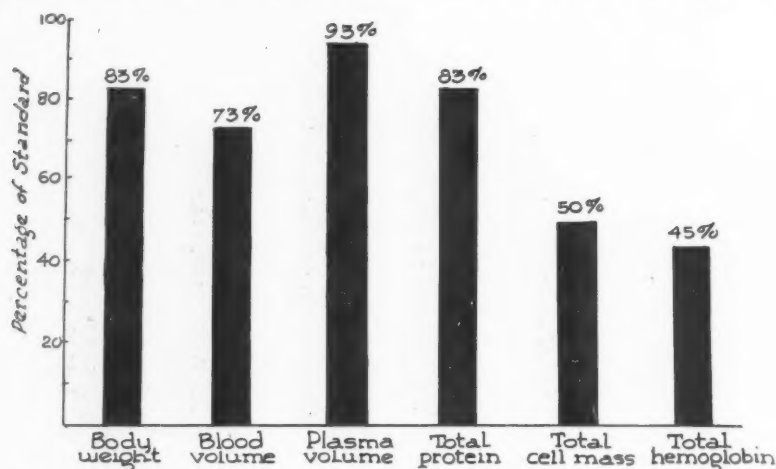


FIG. 7.—Blood volume determinations in carcinoma of the stomach or lower portion of the esophagus. Averages for ten cases.

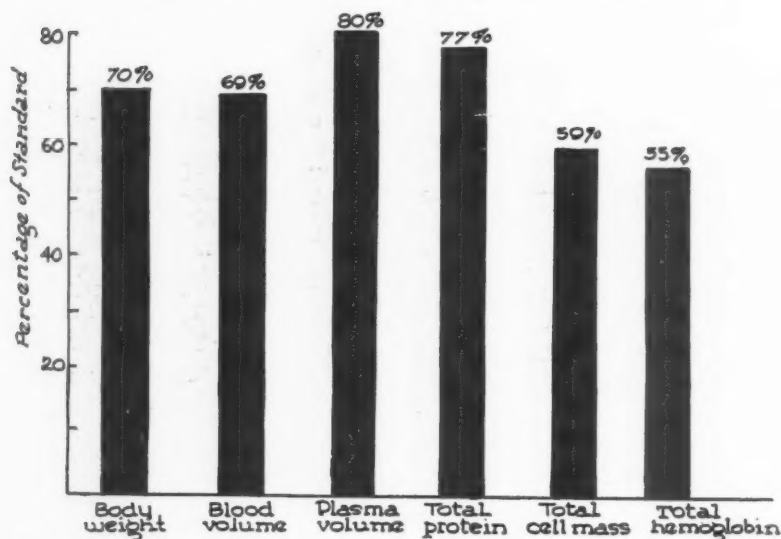


FIG. 8.—Blood volume determinations in carcinoma of the pancreas. Averages for six cases.

328, 333 and 334) the plasma volume was not significantly reduced. The averaged values, as shown in Figure 10, again emphasize the greater deficit in cell mass and hemoglobin as compared to plasma protein.

V. Miscellaneous Malignancies: The studies on these eight patients are

CHRONIC SHOCK

summarized in Table XIV. The findings are of interest, insofar as they illustrate the greater deficiency of hemoglobin as compared to plasma protein.

Discussion.—The deficits observed in patients with malignant disease of the lower portion of the esophagus, the stomach, pancreas, and colon were

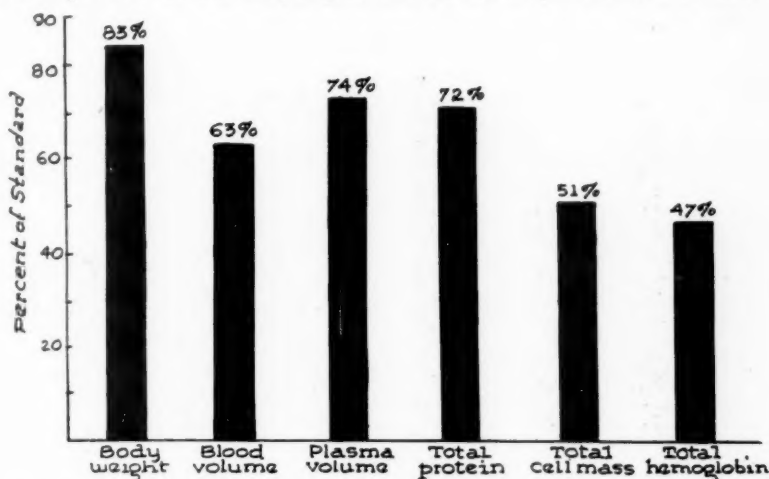


FIG. 9.—Blood volume determinations in carcinoma of the colon. Averages for four patients.

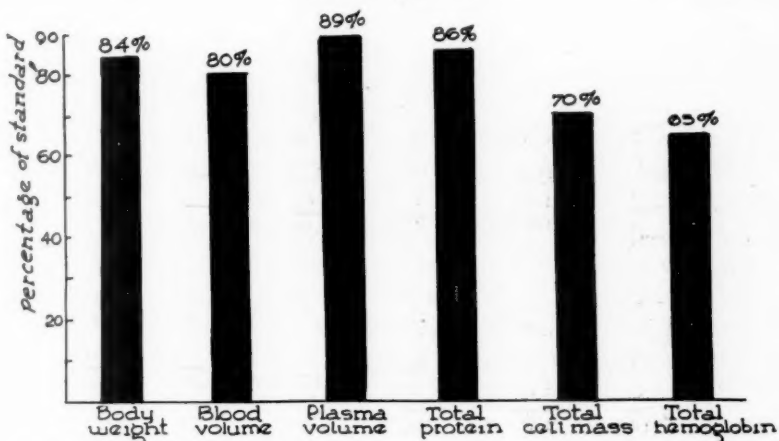


FIG. 10.—Blood volume determinations in carcinoma of the lung. Averages for ten patients.

essentially of the same magnitude. However, as would be expected, the deficits in patients with carcinoma of the lung were less marked. In this condition bleeding is less frequent, and there is no direct interference with nutrition.

It is apparent from our studies that the major factor responsible for the reduced blood volume is a deficiency of total circulating red cell mass and hemoglobin. These findings are in agreement with those of Taylor, and his colleagues,^{20, 21} who reported evidence that tumor tissue implanted into mice and developing chicks results in marked depression of blood hemoglobin con-

centration in the host. These authors²² also reported an early decrease in blood volume associated with a progressive decrease in total hemoglobin when tumor tissue was implanted into mice.

TABLE XIV
MISCELLANEOUS MALIGNANCIES

Case No. and Diagnosis	Weight	Hem- atocrit	Total Hemo- globin Percentage of Standard for Usual Weight	Total Plasma Protein	Plasma Volume	Total Cell Volume	Blood Volume
309—Osteosarcoma, with pulmonary metastases.	79	72	48	96	99	60	82
310—Angiosarcoma of femur.	86	62	40	110	105	41	77
319—Lymphosarcoma.	87	100	75	95	92	83	88
342*—Mycosis fungoides, with multiple metastases.	83	94	67	44	75	67	71
337—Carcinoma of ureter.	78	87	79	95	100	78	90
320—Carcinoma of breast.	100	89	58	100	94	60	78
311—Adenocarcinoma, with liver metastases; primary probably in bowel.	91	95	42	61	60	44	53
301—Adenocarcinoma, with generalized metastases; primary probably in bowel.	62	68	41	98	79	41	60

* 1,500 ML. blood two weeks prior to determination.

The deficit of plasma volume was usually considerably less than that of the red cell mass, and showed a range of from 48 per cent to 123 per cent of standard. Because of this variation the hematocrit proved totally unreliable as an index of the degree of hemoglobin deficit. In general, the plasma volume correlated with the total plasma proteins and gave evidence of maintenance of their usual osmotic affinity. From this it would seem that the changes observed in malignant disease are the result of deficiencies in red cell mass and hemoglobin without consistent depletion of tissue protein reservoirs. Furthermore, since anemia may persist in spite of forced high protein feedings (Patient 314), we are reluctant to accept the point of view of Varco,²³ and others,²⁴ that a high dietary intake of protein is the factor of primary importance in the preoperative preparation of patients with malignant disease. Although this factor is unquestionably of importance, adequate preoperative therapy demands correction of anemia by means of whole blood transfusions.⁵ In malignant disease, as in chronic sepsis,²⁵ there is a fundamental disturbance in hemoglobin metabolism. The nature of this disturbance remains to be elucidated.

SUMMARY

1. Blood volume studies in 38 patients with malignant disease are presented.
2. The major factor responsible for the reduced blood volume associated with malignant disease is a deficiency of total circulating cell mass and hemoglobin.
3. In malignant disease there is a fundamental disturbance in hemoglobin metabolism.
4. Adequate preoperative preparation of patients with malignant disease can be accomplished only by transfusion replacement therapy.

The technical assistance of Miss S. E. Burt is gratefully acknowledged.

BIBLIOGRAPHY

- ¹ Sachar, L. A., Horvitz, A., and Elman, R.: Studies on Hypoalbuminemia Produced by Protein-deficient Diets: Hypoalbuminemia as Quantitative Measure of Tissue Protein Depletion. *J. Exper. Med.*, **75**, 453-459, April, 1942.
- ² Ariel, I., Rekers, P. E., Pack, G. T., and Rhoades, C. P.: Metabolic Studies in Patients with Cancer of the Gastrointestinal Tract: Hypoproteinemia and Anemia in Patients With Gastric Cancer. *ANNALS OF SURGERY*, **118**, 366-371, September, 1943.
- ³ Evans, E. I.: Significance of Blood Volume Alterations in Surgical Patients. *South. M. J.*, **38**, 214-221, March, 1945.
- ⁴ Lyons, C., Mayerson, H. S., Clark, J. H., Nelson, W., and DeCamp, P.: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient: I. Concept of Chronic Shock. (In Press)
- ⁵ Clark, J. H., Lyons, C., Mayerson, H. S., Nelson, W. and DeCamp, P.: Chronic Shock: The Problem of Reduced Blood Volume in the Chronically Ill Patient: II. Hemoglobin and Red Blood Cell Deficits in Chronic Shock. (To be published)
- ⁶ Wintrobe, M. M.: *Clinical Hematology*, Philadelphia, Lea & Febiger, 1942.
- ⁷ Castle, W. B., and Minot, G. R.: *Pathologic Physiology and Clinical Description of the Anemias*, New York, Oxford University Press, 1936.
- ⁸ Oppenheim, A., Abels, J. C., Pack, G. T., and Rhoades, C. P.: Metabolic Studies in Patients with Cancer of Gastrointestinal Tract: Anemia of Patients with Gastric Carcinoma. *J. A. M. A.*, **127**, 273-276, February, 1945.
- ⁹ Kracke, R. R.: *Disease of the Blood*, Philadelphia, J. B. Lippincott Co., 1941.
- ¹⁰ Clark, R. L., Power, M. H., Heck, F. J., and Dixon, C. F.: Iron Deficiency and Anemia Associated with Carcinoma of Proximal Portion of Colon. *M. Clin. North America*, **29**, 958-975, July, 1945.
- ¹¹ Ewing, J.: *Neoplastic Diseases*. Philadelphia, W. B. Saunders Co., 1940.
- ¹² Watson, W. N. W., and Young, C. J.: Failed Splenectomy in Acholuric Jaundice, and Relation of Toxemia to Hemolytic Crisis. *Brit. M. J.*, **1**, 1305-1309, June, 1938.
- ¹³ Jones, E., and Tillman, C.: Case of Hemolytic Anemia Relieved by Removal of an Ovarian Tumor. *J. A. M. A.*, **128**, 1225-1227, August, 1945.
- ¹⁴ Morrison, M.: Analysis of Blood Picture in 100 Cases of Malignancy. *J. Lab. & Clin. Med.*, **17**, 1071-1093, August, 1932.
- ¹⁵ Isaacs, R.: Anemia in Cancer. *M. Clin. North America*, **10**, 1219-1233, March, 1927.
- ¹⁶ Gregersen, M. I.: Practical Method for the Determination of Blood Volume with the Dye T-1824: Survey of Present Basis of Dye Method and Its Clinical Applications. *J. Lab. & Clin. Med.*, **29**, 1266-1286, December, 1944.
- ¹⁷ Evelyn, K. A.: Stabilized Photo-electric Colorimeter with Light Filters. *J. Biol. Chem.*, **115**, 63-75, August, 1936.
- ¹⁸ Barbour, H. G., and Hamilton, W. F.: The Falling-drop Method for Determining Specific Gravity: Clinical Applications. *J. A. M. A.*, **88**, 91-94, January, 1927.
- ¹⁹ Weech, A. A., Reeves, E. B., and Goettsch, E.: Relationship between Specific Gravity and Protein Content in Plasma, Serum and Transudate from Dogs. *J. Biol. Chem.*, **113**, 162-174, February, 1936.
- ²⁰ Taylor, A., and Pollack, M. A.: Hemoglobin Level and Tumor Growth. *Cancer Research*, **2**, 223-227, March, 1942.
- ²¹ Taylor, D. R., McAfee, M., and Taylor, A.: The Effect of Yolk Sac-cultivated Tumors on Hemoglobin Level in Embryonic Chick. *Cancer Research*, **3**, 542-545, August, 1943.
- ²² Taylor, A.: Changes in Hemoglobin Concentration, Total Hemoglobin, and Blood Volume Associated with Tumor Growth. *Cancer Stud.*, Texas Publ., Pp. 95-102, February 15, 1945.
- ²³ Varco, R. L.: Preoperative Dietary Management for Surgical Patients. *Surgery*, **19**, 303-378, March, 1946.

- ²⁴ Lund, C. C., and Levenson, S. M.: Protein in Surgery. J. A. M. A., **128**, 95-100, May, 1945.
- ²⁵ Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army: Report. J. A. M. A., **123**, 1007-1018, December, 1943.

DR. WILLIAM H. PRIOLEAU, Charleston, S. C.: Since hearing Doctor Lyons' presentation of this subject this fall in New Orleans I have endeavored to put into practice his concept of chronic shock. In so doing several questions have arisen, particularly with regard to over-transfusion. In such case what is the fate of the red cells? Is there danger of their breaking down and occluding the renal tubules? Is there an increased tendency toward blood clotting, with resultant occlusion of capillaries?

DR. EVERETT I. EVANS, Richmond, Va.: I rise to comment on Doctor Lyons' paper mainly because of our keen interest for five or six years in the acute shock problem. First, I think we must question the propriety of the term "chronic shock." Those who have suffered castigation at the hands of one or two writers in Philadelphia and New York, know how careful one has to be in the proper use of terms. If we keep in mind what Doctor Lyons is doing, that he is dealing with reduced blood volume, perhaps we can safely use the term, but let us not go back to considering surgical shock as due to many causes.

I should like to refer to our work on 240 patients coming in for more or less routine elective surgery. As we took these patients and estimated their blood volume, the 240 so-called normal patients (whose figures on routine examination showed protein about 7 per cent and hemoglobin about 14.5 Gm.) we found a great number of patients who fell out of the normal range; in other words, some patients can apparently be well and have a plasma volume as low as 19 cc. per kilogram (about 33 per cent of normal). When one considers the total circulating hemoglobin, there may be found even worse situations. Blood volume in some of these patients was so depressed that although many of them showed a normal hemoglobin by routine laboratory test, actually, 85 per cent of these patients had a total circulating hemoglobin below accepted normal values. This simply substantiates everything Doctor Lyons pointed out to you, the extreme importance of estimating hemoglobin according to the total circulating amount and not be falsely led by simple laboratory data for hemoglobin. If you will follow out these plans as laid down by Doctor Lyons, you should be able to operate upon a great many more patients who would not be able to withstand even simple anesthesia without operation if the blood volume were not restored.

I am certain that if you will apply these blood volume methods in your hospital practice, you will improve greatly the postoperative and pre-operative care of patients. Finally, I think that in all teaching hospitals it would be a very good thing if we could interest one or two young surgeons in blood volume technic. I know of nothing that will focus more properly attention on the true causes of cardiovascular failure than attention to or knowledge of blood volume matters. Attention to blood volume and cardiac output data will focus attention properly on physiologic phenomena. In most clinical shock the true cause will be determined and we will not fall into the error of believing it due to errors in technic, toxins, etc.

I think Doctor Lyons is to be congratulated in this important work.

DR. CHAMP LYONS, New Orleans, La. (closing): I am most grateful for the comments of the discussers. I can answer Doctor Prioleau's question by saying we have had trouble in finding enough blood to give to these patients. In general, we have adhered to a daily limit of 1,000 cc. of blood for a patient with an hematocrit below 40, and 500 cc. of blood for a patient with an hematocrit above 40, in the absence of concomitant blood loss. In some of our experiments we have deliberately chosen to provide an excess of red blood cells. There has been no evidence of untoward effect or overloading of the vascular system in all our experiences.

THE TREATMENT OF INJURIES OF THE BRACHIAL PLEXUS*

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TRAUMATIC LESIONS which involve parts of the brachial plexus are not uncommon in civilian and military life. They may be the result of penetrating stab or bullet wounds, or more commonly in civil life, are produced by blunt trauma upon the side of the neck with the head flexed far to the opposite side and the shoulder depressed (Fig. 1). Birth palsies result from injury to the brachial plexus or its roots during parturition, especially in breech deliveries, and the mechanism of the trauma is the same. The chief factor is overstretching and traction upon one or more components of the plexus produced by any means which force the head and shoulder apart. The extent of the lesions depends upon the violence with which the nerve roots, cords or trunks have been stretched and pulled (Fig. 2), so that any degree of injury may be found in the same patient extending between the extremes of incomplete physiologic block and complete anatomic interruption of continuity.

Blunt injuries differ from stab or gunshot wounds in that the nerve fibers are not severed in a well-defined place, but are torn apart. The overstretched funiculi may rupture at any point from the origin of the roots from the spinal cord to the most distal portion of the injury. Therefore, some fibers may be avulsed, others torn apart within the nerve trunks, and others overstretched. The resulting clinical symptoms are those of complete and incomplete anatomic or physiologic lesions which cannot and should not be catalogued according to the early classification of brachial plexus injuries into the upper (Erb) or lower (Klumpke) types. We believe it is far more accurate and practical to determine the extent of the paralysis by careful, detailed examinations of the muscles and then place the level of the lesion by a knowledge of the innervation of those muscles (Fig. 3a, b). The progress of recovery can be followed more easily and a final evaluation of the residual lesion can be made accurately.

Rupture is most frequent in those portions of the plexus which are subjected to the greatest stretch, that is in the 5th and 6th cervical spinal nerves. Avulsion of the roots from the spinal cord is less frequent, and when it occurs, spinal cord symptoms are usually present. The lower roots and spinal nerves which contribute to the plexus; *i.e.*, cervical 7, 8 and thoracic 1, are less often injured and exhibit more evidence of spontaneous recovery. In stab

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or bullet wounds, the most exposed portions of the plexus are usually injured; *i.e.*, the 5th, 6th and 7th cervical nerves and the upper trunk of the plexus, in their course from the spinal column between the anterior and medial scalene muscles. In axillary and infraclavicular wounds the individual nerves which arise from the cords of the plexus and the larger blood vessels are more likely to be injured. We have shown experimentally that bullet or other high velocity missiles have an additional concussive effect which may produce varying degrees of paralysis. Thus, immediately following injury, it is practically impossible to determine accurately the completeness of a brachial plexus injury until an interval has elapsed.

Injury to the contributing spinal nerves close to their exit from the intervertebral foramina or to the upper, middle and lower nerve trunks produces a segmental distribution of the motor and sensory disturbances. The paralyzed muscles fall into groups which correspond with the nerve roots

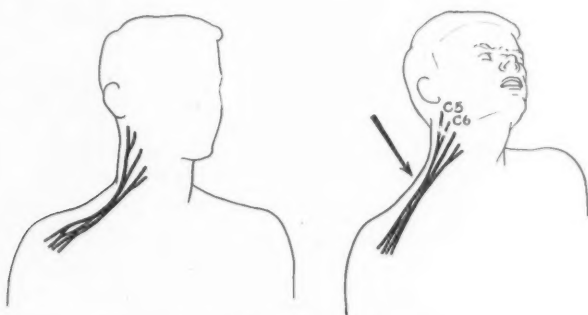


FIG. 1.—Diagram showing the mechanism of production of brachial plexus lesions by blunt injury.

from which they derive their innervation. Thus, injury to 5th and 6th cervical spinal nerves and the upper trunk will affect chiefly the muscles of the shoulder girdle and the upper portion of the extremity. Injuries to the 7th and 8th cervical and 1st thoracic spinal nerves, and middle and lower trunks, produce the greatest disability in the forearm and hand. Injury to the 1st thoracic root or spinal nerve may be accompanied frequently by a Horner's syndrome. Lesions of the cords produce symptoms more closely related to the peripheral nerve pattern of motor and sensory loss. Involvement of the lateral cord produces paralysis in the distribution of the musculocutaneous and upper portion of the median nerves. Medial cord injuries affect the areas supplied by the ulnar, medial cutaneous of the arm and forearm and the lower portion of the median nerve. The radial, axillary, subscapular and thoracodorsal nerves are completely or partially involved depending on the location of the injury to the posterior cord. However, especially in blunt injuries, more than one component of the brachial plexus is involved; trunks or cords may be partly injured and compression and pull may be produced by hemorrhage, infection or an aneurysm. Subsequent extensive scar tissue formation tends to impair

INJURIES OF BRACHIAL PLEXUS

to various degrees many originally uninjured portions of the plexus and gives rise to disseminated and incomplete motor and sensory disturbances.

We have studied 47 cases of brachial plexus injury, 30 of which were produced by high velocity missiles or stab wounds and the remaining 17 by blunt trauma. Twenty-two of the patients were injured in civilian life and 25 while in military service. In six patients there was an associated injury of the spinal cord.

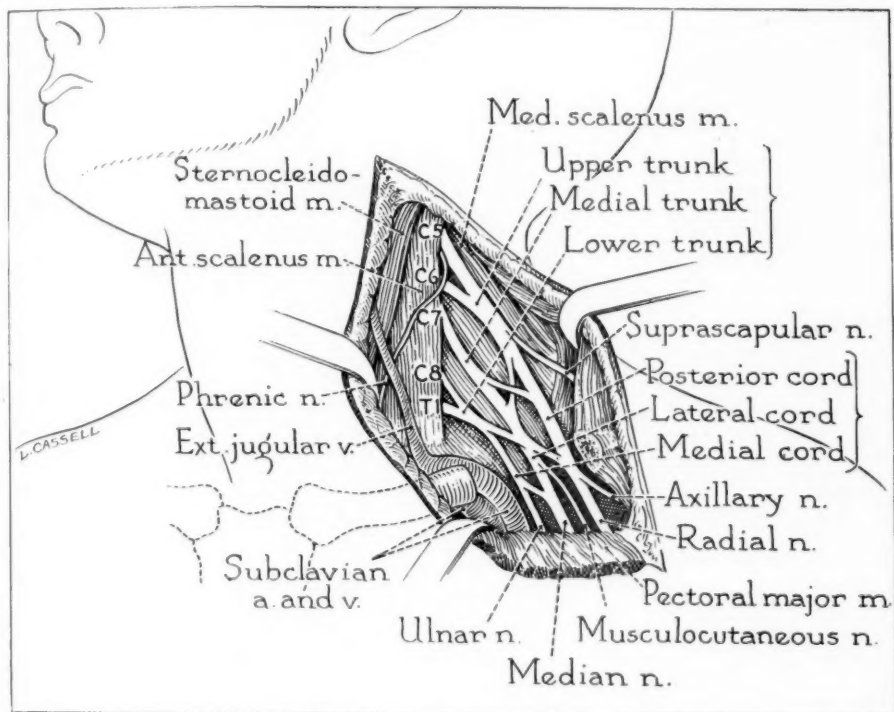


FIG. 2.—Schematic drawing of the main components of the brachial plexus.

The length of time which elapsed between the injury and examination of the patients varied considerably. Usually, lesions due to penetrating wounds were observed at an earlier date after injury than those due to blunt injury, many of which did not seek active medical treatment for periods of three, five and even eight years after injury.

A study of the segmental level of the lesion in this group of patients shows that the 5th cervical fibers were involved 21 times; the 6th cervical 27 times; the 7th cervical 26 times; the 8th cervical 29 times, and the 1st thoracic 18 times. Complete avulsion of the roots from the spinal cord was observed in only two cases following severe automobile accidents and they were associated with spinal cord lesions. Injury to the upper trunk was diagnosed in 11 cases (five blunt, three stab and three bullet injuries), to the upper and middle

trunks in two cases, to the lower trunk in four cases, and to all three in one case. The medial cord was involved in nine cases of gunshot origin; the lateral cord in one case; the posterior cord in four cases; the posterior and lateral cords in two cases, and the medial and posterior cords in four patients. Eleven

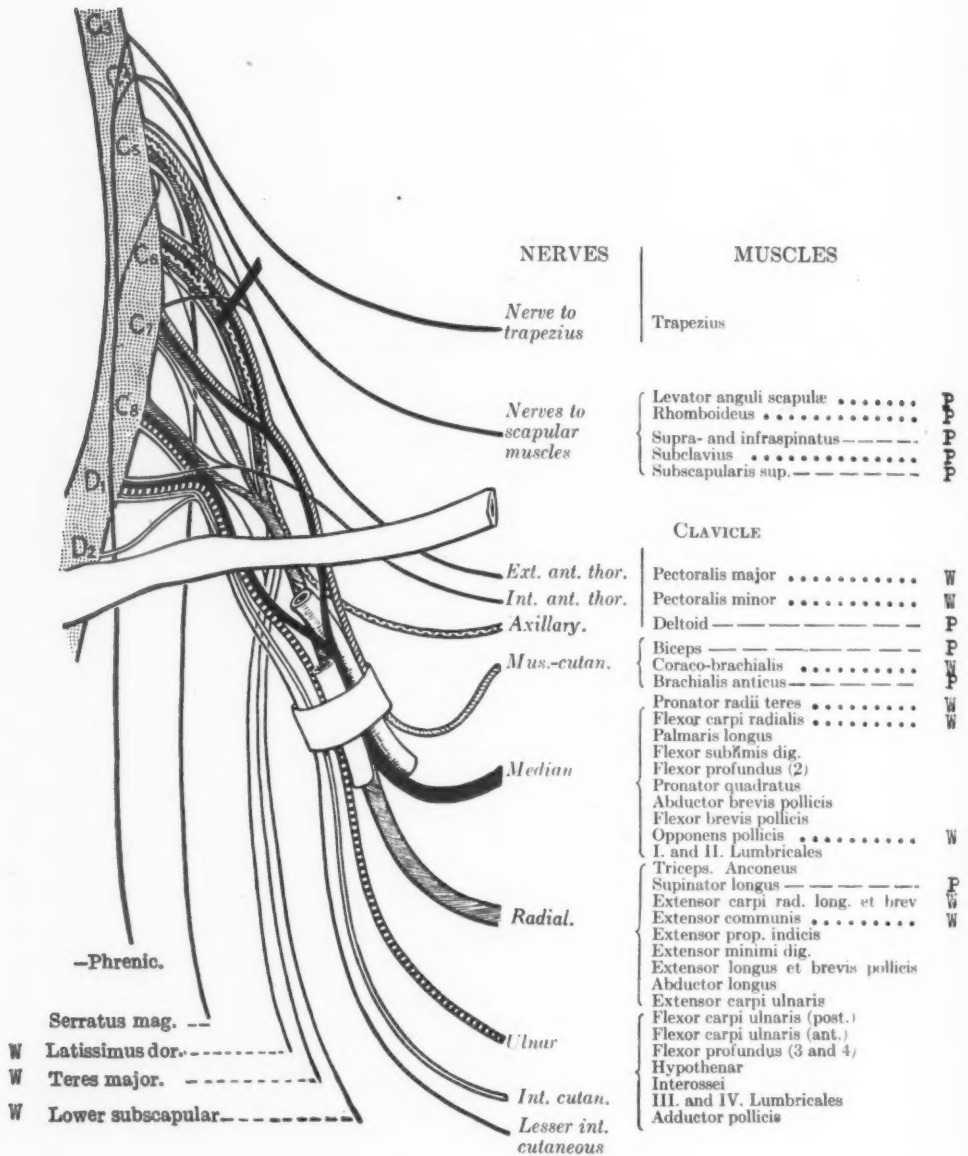


FIG. 3-A

FIG. 3.—(A) Diagram showing the muscles involved in a typical blunt brachial plexus injury.

INJURIES OF BRACHIAL PLEXUS

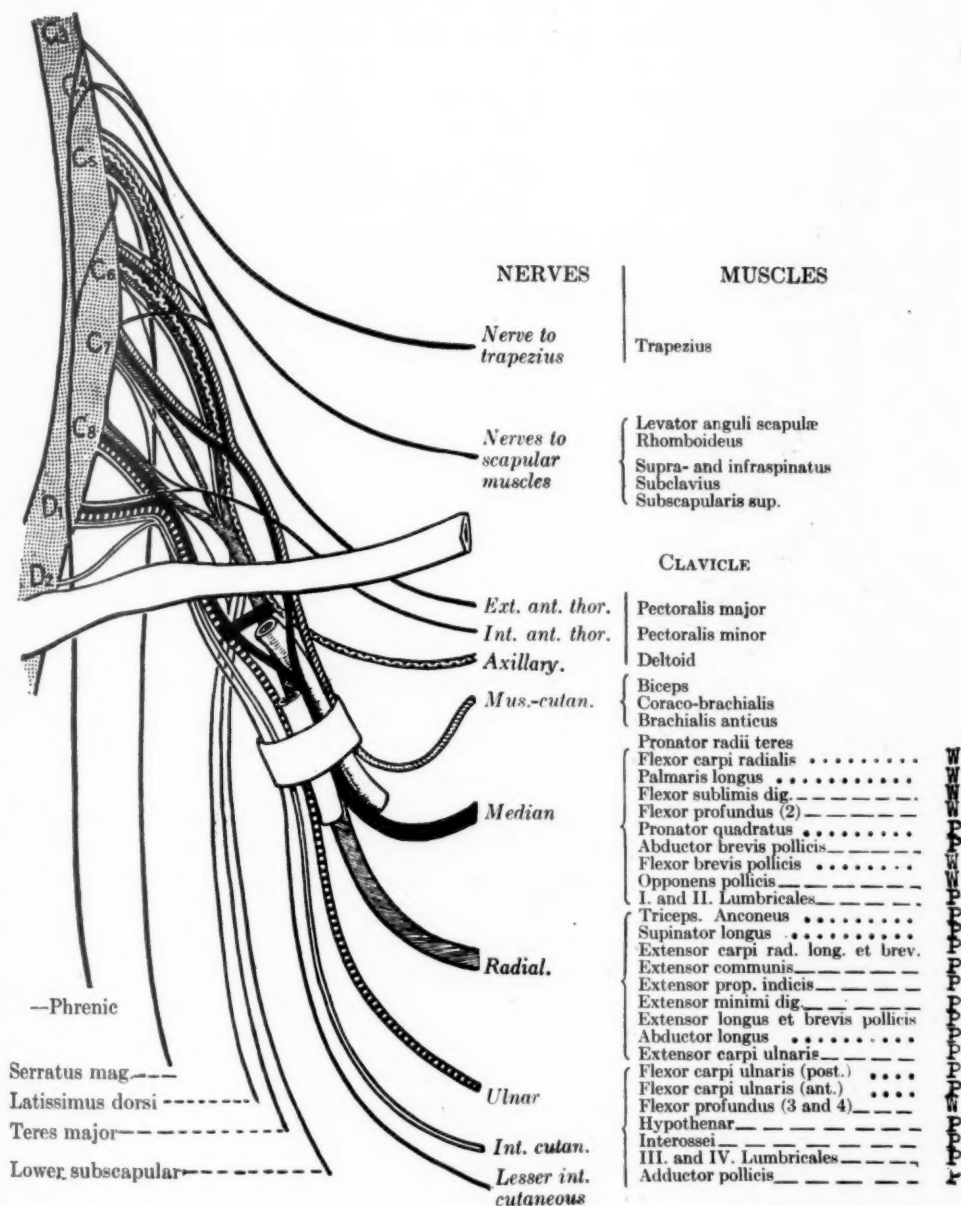


FIG. 3-B

FIG. 3.—(B) Diagram showing the muscles involved in a common infraclavicular gunshot injury of the brachial plexus.

of the lesions to the primary nerves and trunks were due to blunt stretch injuries and in six cases to stab wounds. Blunt trauma caused lesions to the cords of the plexus in five instances only, while 15 were due to gunshot injuries. There was one tardy paralysis involving the ulnar nerve, which was produced by traction on the medial cord of the plexus by the weight of the arm whose shoulder joint had been completely removed by a shell fragment.

Table I summarizes the portions of the plexus found to be injured and the kind of injury reported in this series.

TABLE I
SUMMARY SHOWING PORTIONS OF PLEXUS INJURED
AND THE TYPE OF INJURY

Parts of Plexus Injured	Blunt	Gunshot	Stab
Roots (avulsion).....	2
Nerves, C 5.....	2
C 6 and C 7.....	..	1	..
C 7 and C 8.....	..	1	..
Trunks, upper.....	5	3	3
Upper and middle.....	2
Lower.....	1	2	1
Upper, middle and lower....	1
Cords, lateral.....	..	1	..
Medial.....	..	9	..
Posterior.....	2	2	..
Lateral and posterior.....	2
Medial and posterior.....	1	3	..
Incomplete lesions.....	1	2	..

Associated injuries to the surrounding tissues were frequent. The clavicle was fractured in 11 cases, eight times following bullet wounds and in three instances after blunt trauma. The humerus was fractured and the shoulder joint disrupted in four cases of gunshot injuries. Fractures of part of the 5th and 6th cervical vertebrae were observed in one case following blunt injury and in one bullet wound. Associated severe spinal cord injuries were present in six patients, and in two associated cerebral symptoms were noted. In three cases the recurrent laryngeal nerve was injured on the side of the plexus lesion, and a Horner syndrome was observed in three patients. An aneurysm of the subclavian artery was present in four patients.

As a rule, immediately following the initial trauma to the brachial plexus the entire affected extremity is paralyzed and anesthetic. A physiologic lesion may recover spontaneously and fairly rapidly. In all types of brachial plexus injuries, physiotherapy should be instituted at once and should be systematic and continuous over a long period of time, sometimes years. An attempt should be made to prevent contractures and deformities by proper splinting, massage and passive and active movements. Useful supplementary movements performed by unaffected muscles should be developed and when all evidence of regeneration and spontaneous recovery have ceased, or are unsatisfactory, surgical repair should be considered and carefully evaluated.

The indications for operation on the plexus vary greatly with each individual case and especially when the injury is due to blunt trauma. Signs of spontaneous recovery must be determined for the individual nerve roots and

spinal nerves because the less damaged may regenerate and the more severely damaged ones may show no signs whatever of regeneration. Taylor,⁷ who studied a large group of obstetrical brachial palsies, advised operation six to 12 months after the injury, depending on the amount of spontaneous recovery that had taken place and the severity of the lesion. While a large number of physicians consider brachial plexus lesions as irreparable and hopeless, most neurologic surgeons advise early surgical treatment. The outlook for recovery of function is much improved with prompt surgical repair. As time goes on, scar tissue becomes denser and constricts the plexus more and more, retarding and stopping all possibilities of nerve fiber regeneration. At the same time muscle atrophy progresses, joint changes occur, and in old neglected cases the only method to obtain some function lies in plastic operations upon tendons or joints.

Every attempt should be made to liberate the plexus from the surrounding scar tissue by freeing and identifying the individual roots, trunks, cords and nerves, to resect the scar tissue and neuromas and to obtain an end-to-end union of the ruptured nerves. This is often difficult, and at times impossible, because of the amount of scar tissue and contractions present, especially in old neglected lesions, or when the roots are avulsed from the spinal cord or torn within or near the intervertebral foramina. The experimental promise of properly used nerve grafts is particularly applicable to these injuries. The use of nerve grafts may be indicated where a loss of nerve substance is present and when end-to-end apposition is not possible. Autogenous grafts of the desired size are rarely available and consequently fresh homogenous grafts should be used. In some instances resection of the middle third of the clavicle will make it possible to secure a better end-to-end apposition of the severed nerve segment. It has also been suggested that the severed distal segments of the 5th or 6th cervical roots which can not be sutured to their proximal segments, be sutured to the sectioned ansa hypoglossi. At operation, the entire brachial plexus should be explored, the anterior scalene muscle and the clavicle divided if necessary, and proper electrical stimulation of the exposed nerves employed to detect the injured nerves. Neurolysis was performed in 20 of the 22 civilian patients and in three, end-to-end suture of the severed 5th cervical spinal nerve, or the upper trunk was performed. Bone and metallic fragments which encroach upon the plexus should be removed, and in our cases of aneurysm of the subclavian artery, the artery was ligated without any untoward effect.

In old neglected lesions, the scar tissue may be so dense that even neurolysis becomes impossible and the segments of the severed nerves can not be identified, or the plexus roots are avulsed from the spinal cord making suture impossible. In such cases no improvement in function can be expected from the exploration of the brachial plexus. However, other surgical procedures should be used to obtain the optimal position of function for the extremity. The most gratifying result follows the shortening of tendons of paralyzed muscles or the implantation of tendons of normal muscles into the distal tendons of paralyzed muscles. These plastic operations help to bring the hand,

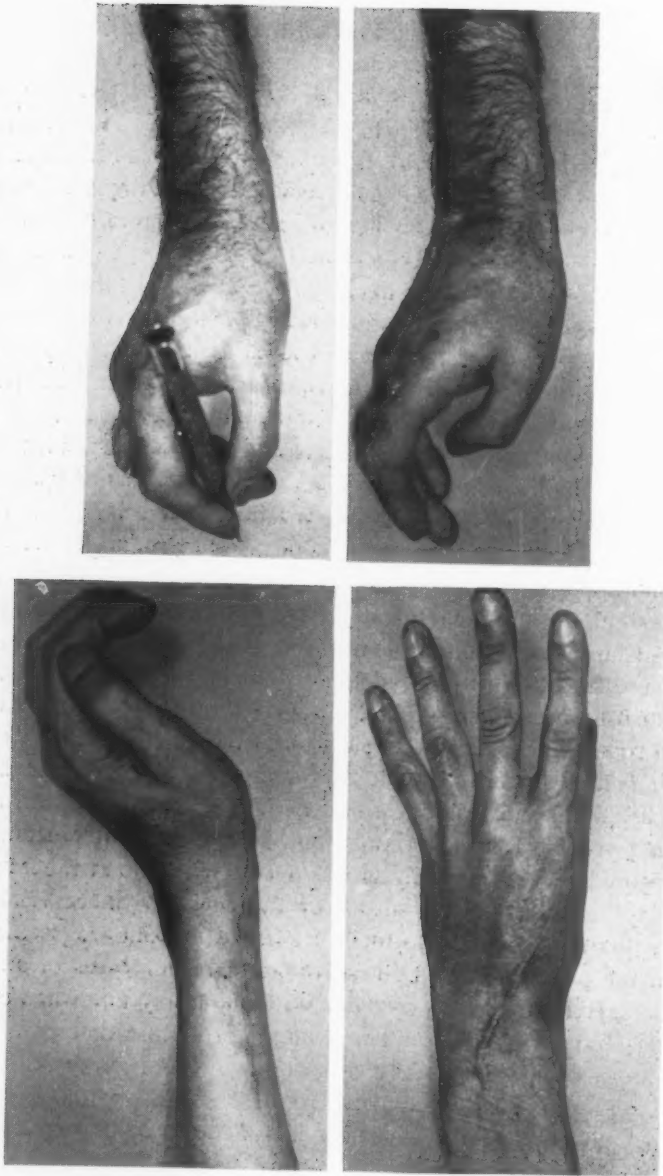


FIG. 4.—Position of function of the hand following tendon transplantations to overcome paralysis of the extensor muscles of the fingers and wrist.

INJURIES OF BRACHIAL PLEXUS

for example, into a position of optimal usefulness, or may bring about some dorsiflexion in a hand of an extremity in which all of the extensor muscles are completely atrophied and fibrosed. Shortening of the tendons of overstretched paralyzed muscles and implantation of normal tendons into paralyzed ones has been undertaken in five of the 47 patients. They all had irreparable injuries of several years' duration—two of them of eight years' duration—and

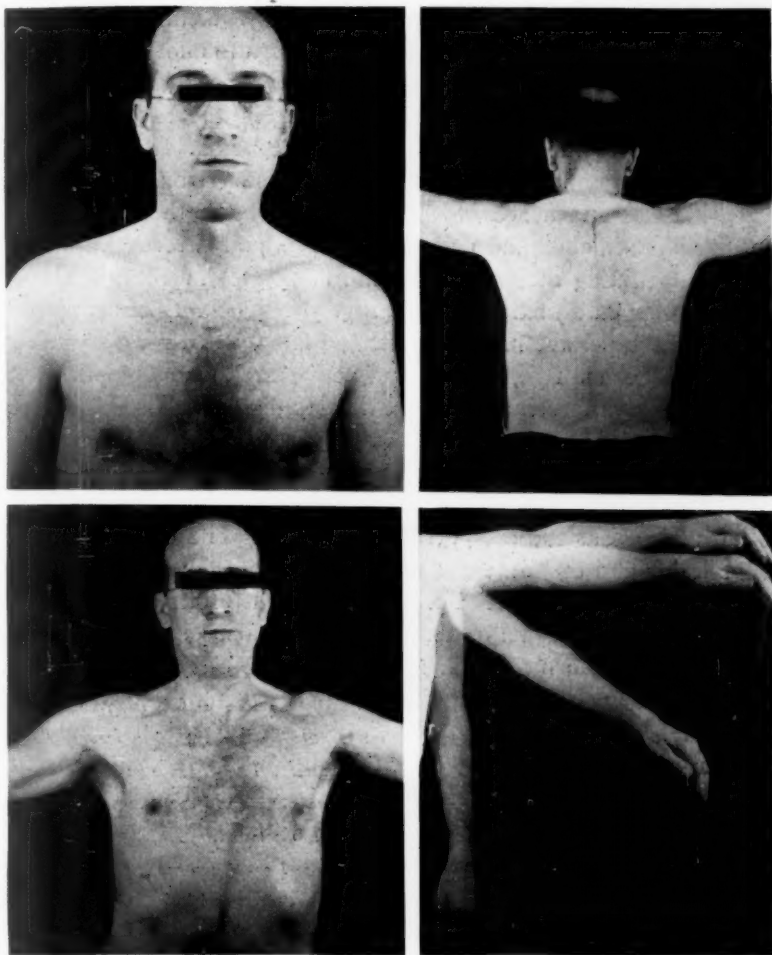


FIG. 5.—Supplementary movements which permit abduction of the arm following a lesion of the 5th and 6th cervical nerves, with paralysis and atrophy of the deltoid muscle.

were, thus, able to develop supplementary movements which greatly improved the function of an otherwise useless extremity. One of them was a 27-year-old male who had a complete paralysis below the 5th thoracic level, due to a severance of the spinal cord, and who also had an irreparable lesion of the posterior cord of the right brachial plexus which resulted in a complete

paralysis of all the extensor muscles of the forearm and hand. He had good function in the flexors of the hand and fingers. The distal tendon of the flexor carpi ulnaris was sutured into the distal tendons of the paralyzed extensor digitorum communis and extensor digiti quinti, the tendon of the flexor carpi radialis was sutured into the distal tendons of the paralyzed extensor pollicis longus and brevis and abductor pollicis, and the tendon of the pronator teres was implanted into the distal tendon of the paralyzed extensor carpi radialis. This procedure gave the patient a useful hand, weakening only slightly the flexion movements but producing enough extension to allow him to write, hold objects in his hand and use them in an adequate manner (Fig. 4).

Physiotherapy is of the utmost importance in the care of the involved extremity, with or without surgical repair of the lesion. Its aim is to prevent the weight of the paralyzed portion of the extremity from overstretching the paralyzed muscles and nerves, to improve the tone of the skin and muscles, to keep the joints mobile and prevent ankylosis and deformities, and to help motion by substituting the use of normal muscles for movements usually performed with the paralyzed muscles (Fig. 5). These treatments consist of light massage and passive motions first, and later, when recovery takes place, of more extensive massage, passive and active exercises. A splint should be worn as long as overstretching or contractures of muscles is not overcome by either recovery of function in the paralyzed muscles or the development of adequate supplementary movements.

The results of the surgical treatment of brachial plexus lesions are, on the whole, not as good as those of peripheral nerves. The distance between the site of the lesion and the muscles and skin involved makes nerve regeneration a slow and prolonged process. Therefore, the end-results should not be evaluated finally for several years after repair. It is also obvious that neurolysis and nerve suture performed upon the plexus can not be done as extensively and accurately as upon a single peripheral nerve trunk. However, Foerster,¹ who performed 29 sutures and 17 neurolyses on 39 patients, reported satisfactory results in the majority of them and, in many instances, complete recovery. He reported failures in three cases of suture, and in three other cases he was not able to suture the nerve trunk following too wide a resection of neuromas. Six of our patients, who were injured in civilian life, have had careful and accurate follow-up examinations over a long period of time, and three have had complete functional recovery, one was greatly improved, and two showed little improvement. The majority of the civilian patients in the series came under our care too long after injury, when the effector mechanisms had been totally destroyed by fibrosis and ankylosis. An insufficient length of time has elapsed in many of the patients injured in military service, and the follow-up mechanism is not functioning sufficiently well as yet, to report accurately upon the results of the treatment in these patients. Estimations of the recovery of function in all peripheral nerve surgery must be based upon the recovery of sensation in isolated areas of supply and upon the recovery of movement in muscles whose action cannot be imitated by supplementary movements.

INJURIES OF BRACHIAL PLEXUS

It is our opinion that the best possible results following brachial plexus injuries may be obtained by operation as soon as the acute effects of injury to the soft parts have subsided. During this interval full advantage must be taken of physical therapy. Then, patients with any residual paralysis should be operated upon. Depending upon the character of the lesion found, all scar tissue should be excised, and, if possible, resection of the neuromas and end-to-end suture of the divided nerves should be performed. If end-to-end suture is not possible without undue stretching, there is sufficient experimental evidence to justify the use of fresh homogenous grafts for the bridging of continuity defects. The surgical treatment of complete avulsions of nerve roots is hopeless. In irreparable nerve lesions, tendon shortening and tendon transplantations should be performed.

REFERENCES

- ¹ Foerster, O.: Die Therapie der Schussverletzungen der Peripheren Nerven. Lewandowsky, Hdb. d. Neurologie, Ergänzungsbd. Chap. 3, Berlin, 1929.
- ² Heidrich, L., and Kuettner, H.: Die stumpfen Verletzungen des Plexus Brachialis. Dtsch. Zsch. f. Chir., **23**, 586, 1931.
- ³ Perthes, G.: Supravaginale Sehnen transplantation bei irreparabler Radialislahmung. Zbl. f. Chir., **44**, 717, 1917.
- ⁴ Pollock, L. J., and Davis, L.: Peripheral Nerve Injuries. P. Hoeber, New York, 1933.
- ⁵ Scaglietti, O.: Über die Operationstechnik der Verletzungen der Wurzeln des Plexus Brachialis durch Schusswaffen. Zbl. f. Neurochir., **7**, 129, 1942.
- ⁶ Stookey, B.: Surgical and Mechanical Treatment of Peripheral Nerves. W. B. Saunders, Philadelphia, 1922.
- ⁷ Taylor, A. S.: The Brachial Birth Palsy. In Dean Lewis' Practice of Surgery, Vol. III, Chap. 7, W. F. Prior & Co., Hagerstown, 1929.
- ⁸ Taylor, A. S., and Casamajor, L.: Traumatic Erb's Paralysis in the Adult. ANNALS OF SURGERY, **58**, 577, 1913.

DISCUSSION.—DR. BARNES WOODHALL, Durham, N. C.: Doctor Davis has presented one of the most perplexing and difficult problems in peripheral nerve surgery. I have nothing but admiration for the context of his paper, and I should like to make simply a few comments concerning certain studies to be carried out in this field in the near future. I am sure that the members of this Association, so many of whom have been interested in military neurosurgery, will be glad to know that the National Research Council and the Veterans Administration have now embarked upon a long-time study of nerve regeneration in injuries sustained in the recent war. I am particularly happy to announce that Doctor Davis and Doctor Pollock, and others of their groups in Chicago, will participate in this study and head one of the five Study Centers. I am sure that we will not only learn a great deal about this phase of military neurosurgery but that we shall also gain some knowledge that can be applied to the treatment of civilian injuries of a similar character.

SHOULD THE NECK NODES BE DISSECTED IN PATIENTS WITH CARCINOMA OF THE LIP?*

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SHOULD THE NECK NODES be dissected as a prophylactic measure, when there is no palpable evidence of malignant involvement? The senior author's early training in Baltimore, at a time when a strong conviction was prevalent, would lead him to answer yes. However, the question is brought up at this time because of an increasing diversity of opinion in the literature and certain facts from our own experience.

To try to get help on this problem from our own perhaps too limited material, we have reviewed the histories of all patients with carcinoma of the lip registered in our Tumor Clinic. As a correlative study, we have also looked-up the patients with squamous cell carcinoma of other parts of the face and scalp. This study was facilitated by our almost perfect follow-up system, which is under the direction of Dr. Arthur B. McGraw.

The Material.—Seventy-nine carcinomas of the lip and 97 squamous cell carcinomas of other parts of the face and head were included in the study, a total of 176 cases. The rarity of carcinoma of the upper lip, and of carcinoma of the lip in the female, was again demonstrated; there was only one clear-cut carcinoma of the upper lip, and only one carcinoma of the lip in a woman. Could rouge or lip stick be a preventive factor? This last fact is more remarkable when it is noted that almost half (42 out of 97 cases) of the lesions elsewhere on the face were in females. The disease is not on the decrease, as will be seen in Table I, which indicates the number of cases seen in five-year periods.

Pathology.—All of the carcinomas of the lip were squamous cell lesions. A few cases indexed as lip lesions were basal cell epitheliomas, but scrutiny showed that they were more properly called carcinomas of the face near the lips. We have assumed that carcinoma of the lips should include only those lesions which have their origin on the vermilion border or at the mucocutaneous junction. Most of the lesions in the series were graded according to the Broder's classification. Thirty were Grade I, 40 were Grade II, two were Grade III, and two were Grade IV. Five were not graded.

Interval before Treatment.—Ten patients had observed the lesions less than 3 months; 10, from 3 to 6 months; 12, from 6 to 12 months; 14, from 1 to 2 years; and 10 for more than 2 years. In 23 patients, a definite history of the interval was not obtained. Fourteen patients had received previous treatment of some sort, including "burning," radiation, excision, and chemo-surgery with zinc chloride (method of Mohs¹).

Methods of Treatment.—In Table II, it will be seen that the treatment of carcinoma of the lip has been chiefly surgical. Radiation in some form was used in a few cases, either as the sole treatment of the primary lesion or as an adjunct to surgery. The cervical nodes were occasionally irradiated,

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CARCINOMA OF LIP

either prophylactically or therapeutically. The operation upon the lip was usually a V-excision, but where the growth was large, the usual plastic procedures were utilized. The neck dissections were limited to the suprahyoid region—the so-called upper neck dissection.

TABLE I
CARCINOMA OF THE LIP

Five-year Periods	No. of Cases
1920-1924.....	4
1925-1929.....	12
1930-1934.....	5
1935-1939.....	14
1940-1944.....	26
1945-.....	18
Total.....	79

TABLE II

Method of Treatment	5-year Cures	3-year Cures	Followed Less than 3 Years but Well	Died of Cancer, or Alive, with Recurrence	Lost or Died of Intercurrent Disease Before 5 Years	Total
Local excision only.....	10	5	18	0	0	33
Excision and radiation.....	5	..	1	..	1	7
Radiation only.....	2	..	1	1	1	5
Excision recurrent tissue.....	3	..	3
Excision and immediate neck node dissection.....	10	3	5	5	..	23
Excision, neck node dissection and radiation.....	1	..	1	3	..	5
Radiation and late dissection neck nodes.....	1	2	..	3
Totals.....	29	8	26	14	2	79

The results of the several forms of treatment are tabulated in Table II. Most of the categories of treatment contain too few cases to make it sensible to compute percentages of five-year cures. Nevertheless, it may be stated that there have been no deaths from cancer in those cases selected for treatment by excision only. There were 15 five-year cures and an additional five patients who were well at least three years after the simple operation. There were eight cancer deaths among 28 patients who had excision plus neck node dissection. It should be noted that at least one of the patients who had a late neck node dissection after the primary lesion was treated elsewhere was a five-year cure.

Thirty-one patients had lymph node dissections, and the results in this group are shown in Table III. The nodes were microscopically-positive in only 7 of the 27 cases in which the procedure was done at approximately the same time as the primary operation. Apparently, the operation was unnecessary in the 20 patients in whom the nodes were negative. It is notable that four of these patients subsequently died of carcinoma, hence, the operation does not appear to give a high degree of protection. One of these four patients died of generalized abdominal metastases, without evidence of recurrence in the lip or neck.

It happens that there were no operative deaths among the 31 neck dissections for carcinoma of the lip, but the only time the procedure was carried out for carcinoma of the cheek, an operative death resulted. The cause of death was asphyxia from laryngeal edema and hemorrhage. Incidentally, the

nodes which were removed at the unfortunate operation were microscopically-negative for malignancy. Others have reported alarming mortality rates, such as 11.4 per cent,² and 6.9 per cent.³ On the other hand, there is a series reported in which there was only one death in 549 operations—a remarkable record.⁴

TABLE III

	Total	Lived	Died Ca.
Immediate dissections:			
Nodes negative.....	20	16	4
Nodes positive.....	7	3*	4
Late dissections:			
Nodes positive.....	4	1	3
Totals.....	31	20	11

* One 20-year cure; one 3-year; and one 1-year.

Only three patients are alive who had positive nodes removed. One of these is a five-year cure. He is well 20 years after operation. However, this procedure was not done as a purely prophylactic measure, since the history states that the nodes were palpable and carcinoma was suspected. The operating surgeon states that it was his policy, at the time, not to remove the nodes unless he thought they were involved. There was a three-months delay between the primary operation and the neck node dissection in the patient with the three-year cure. We have been unable to establish, with certainty, whether the surgeon believed these nodes to be malignant before operation. In the case of the patient who has been followed for one year, the nodes were palpable at the time of operation. The lip lesion was large, measuring 3 cm. x 4 cm.—a neglected tumor.

A review of the literature on the subject reveals a divergence of opinion regarding the advisability of routine node dissection. Three years ago, in a paper read before the Southern Surgical Association, Brown and McDowell,⁵ of St. Louis, stated: "It is thought that the rule should be to undertake dissections in patients with primary carcinoma of the lip or mouth. Deviations of care of individual patients should be away from this rule rather than making it a last resort." This seems to be the attitude of the Mayo Clinic, since New⁶ said: "If definite epithelioma of the lower lip can be determined clinically, I feel that it is better to perform a wide V-shaped excision, which should be followed by removal of the lymph nodes of the neck."

Holding opposing views are such writers as Martin⁷ of the group at Memorial Hospital in New York. He stated: "We do not agree with the principle of giving prophylactic treatment to the neck either by surgery or radiation in the absence of palpably involved nodes." A recent study of 56 five-year cures, by Whitcomb,⁸ of Philadelphia, caused him to remark: "Prophylactic treatment of the lymphatics of the neck by surgery or roentgenotherapy is not necessary because most cancers of the lip do not develop metastatic nodes. Follow-up examination of the neck is the ideal form of treatment." Taylor and Nathanson,⁹ of the Huntington Memorial Hospital, operated by the Cancer Commission of Harvard University, studied 616 cases, of which 411 patients had neck dissections. They concluded: "In cases without palpable lymph nodes or with lymph nodes less than 1 cm. in size,

CARCINOMA OF LIP

provided this group of cases can be followed carefully, there does not seem to be sufficient likelihood of the development of cervical metastasis to warrant routine dissection."

The results reported by some centers using only radiation are impressive. For example, Schreiner and Christy¹⁰ has a 93.9 per cent cure-rate among the determinate cases in 334 patients in whom there were no palpable nodes, and 85 per cent-rate where there were nodes, some of which were thought to be malignant. Radiation treatment is preferred at the New Haven Hospital, according to a report by Lawrence and Oughterson.¹¹ Lymph nodes are dissected only if they are palpable.

It is frequently stated that if one routinely removes the axillary nodes in carcinoma of the breast, one should be consistent and remove the cervical nodes in carcinoma of the lip. However, it is not unlikely that carcinoma of the lip is more like carcinoma of other exposed parts of the face (nose, chin, cheek, *etc.*) than it is like carcinoma of the breast. In our series of 97 squamous cell carcinomas of these parts of the face, a strictly prophylactic dissection was done in only one case, and that patient died an operative death (edema of the larynx). The results of conservatism in the other cases were excellent, since 90 per cent of the cases followed five years were well, and 96 per cent of those followed three years were well. Only the long-standing, neglected cases were not cured by adequate excision of the primary tumor.

In conclusion, we will state that we do not claim to have the final answer to the question propounded in the title to this paper. However, as a result of this study, we have adopted the policy, for the time being, that it is unnecessary to carry out neck node dissections in patients with small, early carcinomas of the lip, if there is no palpable evidence of node involvement. However, such patients will be followed carefully, the neck being examined every month for one year, and every two months for the second year. If a metastatic node appears, a dissection will be undertaken.

REFERENCES

- ¹ Mohs, F. E.: Chemosurgical Treatment of Cancer of the Lip. *Arch Surg.*, **48**, 478, June, 1944.
- ² Kennedy, R. H.: Epithelioma of the Lip: With Particular Reference to Lymph Node Metastasis. *ANNALS OF SURGERY*, **99**, 81, 1934.
- ³ Eckert, C. T., and Petry, J. L.: Carcinoma of the Lip. *Surg. Clin. N. A.*, 1064, October, 1944.
- ⁴ Figi, F. A.: Epithelioma of the Lower Lip. *Surg., Gynec. & Obst.*, **59**, 810, 1934.
- ⁵ Brown, J. B., and McDowell, Frank: Treatment of Metastatic Carcinoma of the Neck. *ANNALS OF SURGERY*, **119**, 543, 1944.
- ⁶ New, G. B.: Malignant Disease of the Mouth and Accessory Structures. *Am. J. Surg.*, **30**, 46, 1933.
- ⁷ Martin, H. E.: Treatment of Cancer of the Lip. *Am. J. Surg.*, **30**, 215, 1935.
- ⁸ Whitcomb, C. A.: Cancer of the Lip: A Study of 56 Five-year Cures. *Am. J. Surg.*, **63**, 304, 1944.
- ⁹ Taylor, G. W., and Nathanson, I. T.: Evaluation of Neck Dissection in Carcinoma of the Lip. *Surg., Gynec. & Obst.*, **69**, 484, 1939.
- ¹⁰ Schreiner, B. F., and Christy, C. J.: Results of Irradiation Treatment of Cancer of the Lip: Analysis of 636 Cases from 1926-1936. *Radiology*, **39**, 293, 1942.
- ¹¹ Lawrence, E. A., and Oughterson, A. W.: Carcinoma of the Lip at the New Haven Hospital, 1921 to 1940. *Conn. State M. Soc. J.*, **8**, 353, 1944.

THE PRESENT STATUS OF THE LEG LENGTH DISCREPANCY PROBLEM*

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AS THE TITLE INDICATES the purpose of this discussion is to call attention primarily to what can be done about the short leg rather than to go into the details and complications of various technics.

As our surgical ability improves we find we can do such impossible things as were mentioned in Biblical times. "By thought alone we cannot add a cubit to our stature," is a quotation from the Sermon on the Mount. Yet we can, by painstaking effort, literally and figuratively, by the patient and the surgeon, respectively, increase our height a few inches.

In the first place as we appreciate the natural adjustments that our spine, pelvis, and lower extremity can make with impunity if one leg is shorter than the other, the indication for surgical interference is occurring less and less frequently. As further progress in methods of nonsurgical growth stimulation and retardation are discovered, even less surgery will be required in the solution of this problem where organic discrepancies exist during the growing period.

Of the major deformities of the body, perhaps the short leg as an entity has received less space in the literature than any of the others. The explanation of this probably lies in the fact that until the growth arrest conception was originated by Phemister, both the leg shortening and the leg lengthening elective procedures were of sufficient severity and carried with them enough risk to discourage their routine performance. Now, with the growth arrest technic, if the afflicted child is seen early enough and if the deformity is not too severe, leg equalization can be approximated, with a relatively minor operation properly timed, at growth maturity.

More importance, however, the writer feels, has been placed on the effects of moderate leg length discrepancy than is justified, particularly as regards back pain and the development of scoliosis. A limp is altogether too frequently attributed to a discrepancy when it really is produced by an unappreciated hip deformity or a muscle function impairment rather than an actual difference in length.

Many individuals with as much as two inches, or even more, discrepancy in leg length can walk without a limp, while others with no discrepancy at all, but with some condition such as a mild spastic hemiplegia or even an old-time "sciatic scoliosis," now known better as one of the discogenetic syndromes, walk with a bad limp, too frequently attributed to a short leg. We usually are fooling ourselves when we employ lifts on heels for mild or fancied

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LEG LENGTH DISCREPANCY

shortening of a leg in a patient with low back pain. They do no harm, however, and often help as a placebo while trying to work out a more rational diagnosis and program of therapy. A great many of us in this audience have a quarter of an inch or more shortening without our being cognizant of it.

In discussing the short leg or the long leg, it is, of course, assumed that all organic or functional deformities have been corrected or at least taken into consideration in deciding a course of action. For example, an adducted ankylosed hip ordinarily should be corrected or accepted for other solution if correction is deemed inexpedient. Likewise, a painless freely movable hip in an adult with two or more inches shortening possibly from a fracture may be better off with a leg equalization procedure than the open reduction ordinarily required. In fixed pelvic obliquities due to a scoliosis such as occurs in severe polio problems, a shortening procedure will frequently be the solution of choice rather than the correction of the more difficult, and not infrequently inoperable, spinal deformity. We must also remember that an ankylosed hip in good position is usually accompanied by a better result than the average arthroplasty.

A technic for measuring leg length discrepancies as accurately as possible should be developed by all surgeons carrying on this work. There is so much chance for error in the conventional tape line measurement from the anterior superior spine to the internal malleolus, that the author feels strongly it should be avoided. A roentgenologic technic has now been used for 12 years, with satisfaction by the author.¹ It consists essentially of taking films of the pelvis with both feet pressed firmly down on a supporting shelf on the table on which roentgenograms are taken. A permanent graphic record of adequate accuracy is thus available for immediate and future reference.

The infrequency of articles appearing in the literature on this general subject until the second decade of the present century shows the formidability with which the surgical procedures were rightfully considered. Both Rizzoli, in Italy, and the elder Sayre, in this country, have been given credit for at least seriously considering the leg length discrepancy problem, but there is considerable justifiable doubt whether in those prelisterian days, *i.e.*, the middle of the 19th century, that they performed the shortening procedures they advocated. Steindler^{1a} gives Rizzoli of Bologna, Italy, undocumented credit for carrying out the idea in 1847. After Codavilla's^{1b} article, in 1905, on leg lengthening, Magnuson's contribution,^{1c} in 1908, was the only one in American literature before 1910. Putti's paper,^{1d} in 1921, laid the groundwork for Abbott's² important contribution six years later, in 1927. Putti, in his 1921 paper, substantiates this statement of Steindler but gives no date and urges anatomic lengthening procedures as more befitting improved surgical technic. Codavilla, appropriately from the Institute Rizzoli, in Bologna, probably read the first paper reporting lengthening procedures in America in 1905, but most of his cases were for malunion of fractures except for one coxa vara. Codavilla is given credit for first using skeletal traction through the os calcis to obtain the required force needed for the correction of these deformities.

The first paper on femoral shortening, in America at least, was written by

Fassett^{2a} in 1918. In it he recommended the step-cutting segment procedure, which the author feels is unjustifiably complicated and which is still being done too often, frequently to the detriment of the patient.

In equalizing leg length differences other than functional adjustments already mentioned, four procedures are possible: First, the long leg can be shortened; second, the short leg can be lengthened; third, in children, the growth of the long leg can be retarded; and, fourth, the growth of the short leg can be stimulated. Generally accepted procedures have been devised for the first three mentioned, but to date no practical method has been contrived to stimulate longitudinal bone growth. It is known that chronic inflammation such as osteomyelitis or even a fracture of the long bones, particularly the femur, will produce enough prolonged hyperemia to materially stimulate growth. In a fracture of a femur in a child, at least half an inch excessive growth can be expected during the year following consolidation, regardless of the amount of actual shortening or deformity that exists.

In most chronic osteomyelitis cases of the lower extremity as well as fractures of the long bones, leg length studies are made at the Shriners Hospital, in Greenville, South Carolina. The greatest difference in leg length attributable to chronic inflammation in observing several hundred cases has been three inches.

The article of Abbott's,² in 1927, was the most detailed scientific treatise on leg lengthening. This was followed by the author's article,³ in 1930, describing a simpler technic, employing the turnbuckle plaster procedure. A fundamentally valuable contribution to the discrepancy problem was that of Phemister's^{3a} on growth arrest, in 1933. Several articles on femoral shortening had appeared before the author's⁴ article, in 1935, but none had advocated the extreme simplicity of the overlap technic before that time.

No paper has yet appeared on the unsolved fourth method of attacking this problem; namely, the stimulation of growth of the short leg. Let us hope that before long some safe, easily and inexpensively-applied procedure may be used to simulate the chronic hyperemia associated with severe trauma and chronic osteomyelitis which has been found to stimulate excessive growth.

The writer, in 1940, did some unpublished animal experimental work on the retardation of growth by heavy roentgen-ray doses, but found, at that time, that the factor of safety between any worth while retardation effect and normal tissue destruction was too limited to make its use justifiable. Barr of Boston, the author understands, is about to publish a report on his experimentation on animals on the possible employment of the roentgen ray for retarding growth. Haas'^{3b} recent contribution on wiring the epiphysis to the diaphysis has been continued by Blount who uses staples instead. The purpose of this work is to use a mechanical means of stopping growth rather than the destruction of the metaphyseal plate and to be able later to release this momentary stoppage and have the growth then continue.

The rationale of Haas' idea, admittedly in the experimental stage, is questioned by the author of this paper, as he feels that the growing force of the

LEG LENGTH DISCREPANCY

entire metaphyseal plate is stronger than the local restraining action of the staples. We are looking forward to Blount's report on the important work he is carrying on along this line.

In discussing the various merits of the three procedures mentioned above, the author is of the opinion that the growth arrest operation on the distal femur, if the age of the patient permits an adequate correction at maturity, is, by far, the most satisfactory, and if done correctly is attended by fewer complications. For over a 12-year period, the author, assisted by various collaborators—four to be exact (Warner,⁵ Stubbins,⁶ Turkell, and Brewer)—have, with satisfaction, performed routinely a modified Phemister technic which has stopped growth at the distal metaphyseal plate of the femur or the proximal metaphyseal plate of the tibia and fibula, or both, as the occasion requires. He still uses the modified Phemister technic, and in only one instance has a deformity sufficient to require surgical correction been recorded. At the start of this work, in our enthusiasm, 12 cases were arrested prematurely, and a similar procedure had to be performed on the "short" side. By employing the simple arithmetical formula for the correction recommended if the operation is done early, satisfactory correction can be expected.

We still figure on three-eighths-inch correction per year on the distal femur and one-quarter-inch on the tibia and fibula, and that, in girls, growth can be expected to stop at 15 years of age and, in boys, at 16 years. Further investigation regarding full height attainment is being carried out at the present time, and it is felt probably that the bone maturation age is put a little low in boys, and it will probably be raised to 17 years. People just seem to grow faster in the south. (Todd's Atlas^{6a} is employed in figuring growth maturation.)

Except for the fact that it must be limited to children, Phemister's contribution, in 1933, is perhaps the most important of all. The simplicity of the procedure merits high commendation although experience has taught us that an exact operation must be done at the right time, and that records more accurate than most clinics are capable of keeping are essential.

Let us hope that, in the not too distant future, some method not requiring hospitalization will be devised that will accurately and safely stimulate hyperactivity of the metaphyseal plate on the short side and in larger or different doses retard growth on the long side.

Many points, notably the accurate calculation of the time of the expected cessation of growth, are to be worked out in the growth arrest problem. But it is felt that, at least at present, this is the most appropriate method of solving the discrepancy problem where the age of the patient allows it. Roentgenograms are made six months after the operation for the first year, and then annually after that. During the first year little improvement can be expected as the operation itself on the epiphyseal plate tends to stimulate growth in the other epiphyses particularly. After this, regular correction can be expected until growth ceases or unless some growth-disturbing incident intervenes.

While it, admittedly, occurs rarely, the author believes that a bilateral growth arrest is justified on an individual who, according to family tendencies,

will become excessively tall. He has never done this, but Steel, of Pittsburgh, has done the more drastic femoral shortening.

In a few instances multiple procedures are justified, particularly when the remaining period of growth is not sufficient to allow the retardation rate to be effective in time. Here, both femoral and tibial epiphyses either side of the knee can be arrested simultaneously, and in an occasional case even this complicated procedure can be supplemented by a femoral shortening on the same side.

In performing the femoral shortening on children it must be remembered in figuring the amount of shortening that the very operation is a stimulus to growth and not infrequently a full inch extra growth occurs, nullifying possibly to 50 per cent, the result obtained by the shortening. It is advisable, therefore, when shortenings are done during the growing period that growth arrests should be done at the same time.

While it is true the esthetic disadvantage must be seriously considered, it is strongly felt that the added risk of lengthening procedures, except in the case of rare instances, is not worth taking. A large portion of these cases are in polio cases, where usually the lowered center of gravity improves the general stability of the patient.

In closing, it is felt that at this time the following comments are justified:

1. The best way at present to effect equalization in leg length where a patient is in the growing period is to employ single or multiple growth arrests at a time determined by careful calculation.

2. In adults the femoral shortening procedure is justified in selected cases, even in children, if growth arrests are performed, realizing that the operation carries with it very definite hazards.

3. In children and adults leg lengthening procedures are very occasionally justified even by the experienced surgeon, who carefully balances the definite hazard with the indications.

4. It is hoped that, in the not too distant future, a safe practical method for bone growth retardation and stimulation will be formulated.

REFERENCES

- ¹ White, J. Warren: A Practical Graphic Method, *etc.* S. Med. J. 33, No. 9, 946-949, September, 1940.
- ^{1a} Steindler, A.: Orthopedic Operations. Charles C. Thomas, Springfield, Ill., Second Printing, 1943, P. 237.
- ^{1b} Codavilla, A.: On the Means of Lengthening the Lower Limbs. *etc.* Am. Jour. Orthop. Surg., II, 353, April, 1905.
- ^{1c} Magnuson, Paul P.: Lengthening Shortened Bones of the Leg by Operation.
- ^{1d} Putti, V.: The Operative Lengthening of the Femur. J. A. M. A., LXXVII, 934, September 17, 1921.
- ² Abbott, Leroy C.: The Operative Lengthening of the Tibia and the Fibula. J. Bone and Joint Surg., 9, 128, January, 1927.
- ^{2a} Fassett, F. J.: An Inquiry as to the Practicability, *etc.* Am. Jour. Orth. Surg., XVI, 277, September, 1918.
- ³ White, J. Warren: A Simplified Method for Tibial Lengthening. J. Bone and Joint Surg., 12, No. 1, 90-96, January, 1930.
- ^{3a} Phemister, D. B.: Operative Arrestment, *etc.* J. Bone and Joint Surgery, 15, 1, January, 1933.

LEG LENGTH DISCREPANCY

- ^{3b} Haas, S. L.: Retardation of Bone Growth by Wire Loop. *J. Bone & Joint Surg.*, 27, P. 25, January, 1945.
- ⁴ White, J. Warren: Femoral Shortening for Equalization of Leg Length. *J. Bone and Joint Surg.*, 17, No. 3, 597-604, July, 1935.
- ⁵ White, J. Warren, Warner, W. P. Jr.: Experiences with Metaphyseal Growth Arrests. *S. Med. J.*, 31, No. 4, 411-414, April, 1938.
- ⁶ White, J. Warren, Stubbins, Sam G. Jr.: Growth Arrest for Equalizing Leg Lengths. *J. A. M. A.*, 126, 1146-1148, December 30, 1944.
- ^{6a} Todd, T. Wingate: *Atlas of Skeletal Maturation*. C. V. Mosby Co., St. Louis, 1937.

DISCUSSION.—DR. R. W. JOHNSON, Baltimore, Md.: I have been much interested in Doctor White's paper, because I have always felt he had the last word to say about epiphyseal arrests and shortening. I have fortunately been in the middle ground, as I also admire Roy Abbott's bone lengthening technic, which is a beautiful surgical procedure. I have done both, and at the cost of some labor and much anxiety; I think both have their uses and indications and contraindications. I would *rather* do a shortening or arrest procedure. I think it is easy, and simplest of all in the polio cases when you get the patient young and know what the shortening will be. I think this arrest procedure as performed by Doctor White is best, and in the later cases I think his bone shortening also offers the most simple procedure. But the Abbott operation has a definite place in polio cases where most of the shortening is in the tibia below the knee, where it becomes so much shorter compared to the other leg and to the upper leg as well. These cases with very little tissue in the calf muscles give an opportunity to get lengthening without loss of muscle power, and here, to my mind, leg lengthening is the procedure of choice.

I often lose heart myself in this operation's convalescent period, because it seems a formidable procedure, with turning turnbuckles, *etc.* But when you ask the patients at the end of a year whether they feel it is worth while, they all seem to feel it is. So I think we must balance the procedure against the ultimate results for the patient, and choose carefully between "good leg" shortening and "bad leg" lengthening in the polio cases especially. I do not think a full-muscled leg should ever be lengthened.

DR. BRADLEY L. COLEY, New York City: One measure that can be taken by the profession to prevent unnecessary shortening of a limb is to avoid the use of roentgen-ray therapy for bone cysts and other benign lesions of bone occurring near the epiphysis in children during the period of bone growth. We have seen a number of instances in which such use of roentgen-ray therapy (this was in the early days when it was widely used for a variety of bone lesions, both benign and malignant) was followed by considerable shortening. Unless one follows these children to maturity the importance of this interference with bone growth may be overlooked.

While such an event is no doubt comparatively rare, we have observed three cases of bone cyst, followed for periods of from 12 to 15 years after roentgen therapy, which developed sarcomatous alteration in the involved area. In two of these cases an interscapulothoracic disarticulation had to be performed, and in the third, pulmonary metastasis occurred before a hipjoint disarticulation could be considered.

DR. J. ALBERT KEY, St. Louis, Mo.: I want to ask Doctor White how late in life he does this overlap. It seems to me that if a child is young enough for an overlap an epiphyseal arrest is indicated.

Where shortening is indicated I prefer a step-cut or oblique resection. My last shortening was done with a Blount blade plate. This was in a large girl, age 19, and the operation was quite difficult.

DR. PAUL B. MAGNUSON, Chicago, Ill.: Having become a bureaucrat, I do not know whether I should say anything about surgery, but I did my first leg lengthening operation some 30 years ago, and that patient promptly died. I used very bad judgment in that case; the child was too young and I did not have the proper apparatus. There was too much hemorrhage and shock. After that I confined my attention to leg length-

ening on older patients. I like the step-procedure, but I do not trust to cross strain-bearing screws without any provision for end-bearing thrust to resist the pull of muscles. I do not think one can counteract the pull of the strong muscles in the leg without some form of plug between the ends of the fragments. Doctor White's case in which the screws were broken is an example of what the muscles of the thigh will do if they are allowed to work 24 hours a day without countertraction, and if countertraction is not provided the pull of the muscles will break almost anything which is put in.

I feel that I have done my last leg lengthening operation. It is more sensible to do a growth arrest. I do not think either patient or doctor gets much satisfaction out of one inch difference following operation. I have lengthened legs more than that; in three, toe drop resulted—which finally cleared up—but I do not think the amount of lengthening that can be attained safely pays for the risk and the amount of agony to which the patient is subjected. It is much safer to have a growth arrest or a shortening operation on the other leg. I see no reason for doing a lengthening operation of this sort on growing children. When growth is attained the bones are easier to handle, shock can be more easily dealt with, and one can actually judge whether it will be worth while to level the patient's pelvis by lengthening one leg or shortening the other. I do not think we want to operate unless there is assurance of some permanent value to the patient.

Dr. J. WARREN WHITE, Greenville, S. C. (closing): I appreciate these discussions very much, and I think we can answer some of these questions. I am glad to say that Doctor Johnson and Dr. Roy Abbott are still sticking to the leg lengthening procedure more than the rest of us, as I think some of us should still be doing it. I recently asked Doctor Abbott what his opinion was now about this procedure and he said he felt that the lengthening procedure in polio cases should be considered in certain cases. We have also seen the effect of roentgen-ray on a local tumor mass, where growth disturbance has resulted.

Doctor Key is still paying too much attention to the appearance of the roentgenogram. I have had a good many letters from surgeons from various parts of the country, criticizing me for suggesting this shortening procedure, and, in correspondence with them, I have found that they have invariably done more than minimal requirements; the simpler the operation is, the better it is. If we do the step-cutting operation, that means these bone ends have to be accurately shaped so as to make them fit fairly decently. This procedure complicates the operation, and if you know it is going to come out all right, if you do not devote time to that, it is an unnecessary part of the technic and I think it can be safely skipped. In a few years the roentgenograms all look the same.

The oldest overlap procedure I have done is in an individual who went on Saturday night binges too often, and I was tired of repairing pathologic fractures of the femur, as he never seemed to get good solid union. He had lost the other leg, so length compensation could be easily taken care of. I thought that if I reduced his height, he would not be so likely to fracture that bone when he fell. I overlapped it three inches and screwed the bone together. That is five years ago, and I have not heard from him since.

The Blount procedure, which Doctor Key is not so enthusiastic about, I think has a definite place in cases where we want maximum shortening in a large thigh. It is hard to close the wound satisfactorily when the overlap is done in the middle third; there is a mass of muscle difficult to confine in a small space. If a shortening of three inches just below the trochanter is performed, using the blade plate, advantage of the extra space in the upper thigh can be taken, and the wound will come together with much less tension.

In regard to Doctor Magnuson's idea that shortening should not be done in children, I agree with him absolutely, but so often we get these children so late that something more than growth arrest must be done. The growth arrest is not as complicated as Doctor Key seems to think, but it has to be done adequately as well as timed correctly. It is well within the surgical ability of even a surgeon not particularly skilled in these procedures. The solution of the mathematical problem must be done correctly, and should be checked by some other interested surgeon. The final responsibility of these cases should be vested in one member of the clinic staff.

ANALYSIS OF PELVIC OPERATIONS PRECEDING HYSTERECTOMY*

CAUSAL RELATIONSHIP

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THE INCREASE in the number of hysterectomies being performed has become a current source of widespread criticism. It is not my purpose to defend either side of such a controversy but rather to call attention to the number of hysterectomies which have become necessary as a direct result of previous operations upon the pelvic organs. A critical study of 1,048 consecutive cases of hysterectomy performed by me on private patients over a period of 15 years at Touro Infirmary has been made. It was found that previous pelvic operations were directly responsible for the subsequent necessity for removal of the uterus in 436 cases (Table I). This is to say that 41.6 per cent of the total number of hysterectomies performed by me during this period were indicated because previous operations upon the pelvic organs had failed to accomplish their purpose.

It is not my intention to condemn pelvic operations in general. Instead, I would like to call attention to the importance of making a thorough study of the symptoms of these patients before operation and to emphasize the desirability of selecting the surgical procedure which will not only relieve the patient of her symptoms but also obviate the need for subsequent operation as much as possible.

It is, of course, the earnest desire of every surgeon when advising a pelvic operation to relieve the patient of her symptoms but at the same time to preserve the organs of reproduction. However, not one of the 436 patients in this series subsequently became pregnant. Thus, this important function of the uterus was not fulfilled and the uterus remained only to produce a train of symptoms which necessitated a second operation. It would appear, then, that the wiser course in such cases would be removal of the uterus when the patient originally consults the physician regarding such symptoms.

It seems to me that too much emphasis has been placed on the importance of menstruation. It is true that the function of the uterus is childbearing, with menstruation of secondary importance, but too often we encounter women upon whom the surgeon has performed a pelvic operation in an attempt to conserve the uterus, but he has not corrected the principal pathologic condition, and malignant changes have appeared in the uterus several years later. In this

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series the average time between the previous pelvic operation and subsequent hysterectomy was 4.8 years.

The two complaints most commonly presented by the patients in this series were persistent and increasing pelvic pain and irregular, profuse, intermittent or prolonged vaginal bleeding. Other symptoms complained of less frequently include urinary and rectal discomfort, a sense of pressure in the pelvis and prolapse of the uterus and bladder, leucorrheal and watery vaginal discharge, dyspareunia and sexual disturbances, such as lack of libido and orgasm. These are the same symptoms for which the patient willingly submitted to a previous operation.

TABLE I
PREVIOUS PELVIC OPERATIONS DIRECTLY RESPONSIBLE FOR
SUBSEQUENT HYSTERECTOMY

Indication	Cases	Cases
Salpingectomy:.....		176
Unilateral.....	42	
Bilateral.....	134	
Operations resulting in Stricture of Cervix.....		125
Amputations.....	61	
Cauterizations.....	43	
Conizations.....	21	
Suspension of Uterus.....		62
Radium Therapy:.....		37
Benign.....	30	
Malignant.....	7	
Vaginal Plastic Operations.....		36
Total.....		436

The most frequently performed previous operation was salpingectomy, which was done in 176 of the 436 cases. Despite removal of both fallopian tubes in 134 of these, the patients returned usually with the complaints of pelvic pain and abnormal bleeding, and in some instances malignant changes in some part of the remaining pelvic organs. Would not a more radical procedure in the beginning have been preferable in these cases? It is my opinion that with the improvement in treatment of pelvic infections and the ever increasing knowledge of antibiotics salpingectomy *per se* will become obsolete. In the last ten years I have never removed both of the adnexa uteri without also removing the uterus. There appears to be no justification for ablation of the adnexa only to leave a useless organ such as the uterus which has already become somewhat affected by the previous pathologic process, merely to preserve menstruation, which almost always will become abnormal.

Of the 436 cases complete stricture of the cervix was the direct result of the previous operation in 125 patients. Forty-three of these women had cauterizations of the cervix, 21 conizations and 61 amputations. The indications for the subsequent hysterectomy in these cases were the same as for the previous operations; namely, increasing and irregular pelvic pain and prolonged vaginal bleeding. It is my belief that less radical treatment and more

HYSTERECTOMY AFTER PELVIC OPERATION

diligent postoperative care in these cases would have prevented the eventual necessity for excision of the uterus. In the chronically infected cervix it would seem that light office cauterization would not only eliminate the infection but would obviate the need for a future operation. When conization or cauterization is done, constant observation to prevent future strictures is imperative. In the chronically infected, hypertrophied and eroded cervix no form of amputation will completely relieve the patient and at the same time insure against the possibility of future difficulties. The amputation is either too low to do any good or too high. The danger of stricture is obvious; cervical stricture as an etiologic factor in the subsequent development of pelvic endometriosis or uterine malignancy is too well known to require further comment. There is also the possibility of the development of future menstrual disorders and pelvic pain.

Since the uterus is a naturally freely movable organ, too enthusiastic abdominal shortening of the round ligaments or fixation of the uterus to the parietal wall with resulting adhesions only prepares the patient for future difficulties. In the series under discussion there were 62 cases in which a previous suspension operation either failed to relieve the patient of pain and bleeding or later led to such symptoms that hysterectomy eventually became desirable; in 25 of these 62 cases abdominal suspension had failed to correct a prolapsed uterus. In two cases besides the previous suspension operation, intestinal obstruction necessitated a serious operation before the uterus could be removed.

Thirty-seven of the 436 patients required hysterectomy after radium therapy for benign conditions had proved ineffective. In 30 of these the bleeding was not controlled by the application of radium and in an additional seven cases malignancy of the endometrium developed in the uterus several years following radium therapy. These statistics would indicate the necessity for better judgment in the selection of cases for radium therapy.

The statistics obtained from this study are not offered to encourage the promiscuous performance of hysterectomies. However, if a woman presents symptoms requiring surgical intervention in the pelvis, it is the duty of the physician to select the method of treatment which will not only eliminate the patient's complaints but will at the same time prevent the necessity for future operations and eliminate the risk of subsequent development of malignancies when possible. In many cases the only operation which fulfills these requirements is hysterectomy.

SUMMARY

From a critical analysis of 1,048 consecutive cases of hysterectomy performed upon private patients over a period of 15 years it was found that previous pelvic operations were directly responsible for the subsequent necessity for removal of the uterus in 436 (41.6 per cent) cases. None of these patients subsequently became pregnant. The average interval between the previous pelvic operation and hysterectomy was 4.8 years.

The most frequently performed previous pelvic procedure was salpingec-

tomy. Cauterizations, conizations and amputations resulted in complete stricture of the cervix in 125 patients. Suspension of the uterus, done in 62 cases, only prepared the patients for future difficulties. Hysterectomy had to be done in 37 cases of malignancy after radium therapy proved ineffective.

DISCUSSION.—DR. JOHN C. BURCH, Nashville, Tenn.: Doctor Tyrone has brought to our attention a group of cases with which most of us are familiar. We usually refer to them as "do-overs." If the first, or primary operation, had been conducted along physiologic lines there might have been no necessity for the second.

In approaching a pelvic case, the patient must be individualized and her functional needs ascertained. Then the surgeon can intelligently conserve, if possible, those functions which are useful to that particular patient. Our chief error is usually the conservation of a useless function under the misguided label of conservatism. For example, a 40-year-old, para IV, has an ovarian cyst; we remove it and leave the uterus and opposite adnexa. This is conservative treatment. Leaving the uterus leaves the patient subject to all the menstrual difficulties resulting from primary and secondary ovarian failure. An appreciable number of such patients will subsequently develop a menstrual disturbance severe enough to require hysterectomy. An even larger number will have milder symptoms.

Some time ago when studying glandular cystic hyperplasia, we found it could be consistently produced in animals subjected to partial castration. Daily experience confirms the fact that partial castration in the human leads to hyperplasia. Hence, unless the reproductive function must be conserved, it is wise to consider the removal of the uterus also in those women subjected to partial castration. In my opinion, the remaining ovary will function at its normal level. The watchword of the pelvic surgeon might well be the conservation, not of function, but of useful function.